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CLINICAL NOTES OF CASES OF PERNICIOUS ANÆMIA.[1]

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This paper is intended to be, for the most part, as its title implies, a clinical one. The cases described were studied at the bedside rather than in the laboratory. In their investigation instruments of precision were employed; not so much to determine the numerical relations of histological elements in each individual case as for purposes of diagnosis—in other words, to distinguish the disease pernicious anæmia from other diseases which it may resemble, and especially from latent gastric carcinoma.

In three of the five cases which I now report there were autopsies, and it is to be regretted that no histological studies of the post-mortem specimens were made. For this my responsibility is only indirect, as the examinations were made by the pathologists of the hospital in which the patients died.

Case I. *Profound anæmia, with all the characteristics of the pernicious type; peripheral neuritis, with paralysis of extensors; bronzing of skin, with freckle-like spots upon its surface. Result fatal.*—Annie McC., aged sixty-four years, native of Ireland, domestic; admitted to Philadelphia Hospital, December 29, 1896. Family history excellent. Parents, brothers, and sisters well and strong up to advanced period of life.

History of present illness. The patient was also well and strong, with a good, healthy color, until one year ago, when well-marked gastro-intestinal disturbances set in. These consisted of pain after eating, and frequent vomiting, with diarrhœa, which symptoms have persisted in greater or less degree up to the present time. The vomited matters consisted sometimes of the ingested food; at others solely of bile and mucus. In consequence she has lost much in weight, although is far

[1] Read before the Association of American Physicians, Washington, D. C., May, 1900.

from being "emaciated." During the period mentioned she has lived chiefly on milk, other food aggravating the above-mentioned troubles. There has, however, been almost complete anorexia.

Symptoms on admission. Great weakness and lassitude, shortness of breath, palpitation of the heart and præcordial oppression, with dull, aching pain in the epigastrium. Constriction of the waist, as by corsets, insupportable; cannot partake of solid food; but eggs, milk, and water cause little or no distress. A distinct systolic murmur, loudest at the apex, was heard and considered too harsh to be merely hæmic.

I took charge of the ward containing this patient on February 1, 1897, up to which time the blood had not been examined. The intense lemon-tinted pallor was highly suggestive of pernicious anæmia, and this diagnosis was confirmed by the first blood count, which was made on February 12th.

Number of red cells, 1,050,000 per c.mm.—21 per cent.; hæmoglobin, 25 per cent.; marked poikilocytosis. No estimate of the white cells, either absolute or relative, is recorded in the ward notes.

From this time until the patient's death, on June 23, 1897, the following counts were made:

March 15, 1897. Number of red corpuscles, 500,000; number of white cells, 5200; Hb., 19 per cent.

April 19*th*. Number of red corpuscles, 560,000; Hb., 14 per cent.

May 11*th*. Number of red corpuscles, 938,000; Hb., 36 per cent.; white cells, 3000.

June 18*th*. Number of red corpuscles, 375,000; Hb., 18 per cent.

The eye-ground was examined by Dr. Charles A. Oliver, who reported several hemorrhages scattered over the retina, the larger ones near the periphery.

From the voluminous ward notes of this case it appears that there was marked improvement as regards the digestive disturbances, with, however, occasional inexplicable attacks of diarrhœa and vomiting.

On February 19th the patient began to complain of a tingling sensation and numbness in feet and hands, and on March 3d these pains are recorded as being so severe as to elicit cries of pain.

The following note was made on March 15th: For several days the patient has been complaining of neuralgic pains in the feet and hands, and extending up the arms along the nerve trunks, with gradually increasing weakness and numbness, until to-day there is complete paralysis of extensors of hand and the same condition of those of the feet. She is unable to hold any object with either hand. Fowler's solution, which had been administered in doses of 10–20 drops for three weeks, stopped, the arsenic being regarded as a possible cause of the paralysis. Opposed to the hypothesis of arsenical neuritis is the fact that no gastro-intestinal disturbance had been excited by the drug (on the contrary, that previously existing had subsided) or any œdema of the face. The patient at this date declared herself better, except as regards the neuritis, than for six weeks previously. Her statements are, however, unreliable, her mind being readily open to suggestions. The blood count at this date showed but 10 per cent. of red corpuscles.

April 23*d*. At this date a condition of slight general anasarca was noted, the face being œdematous, especially on the side on which the patient lay, and the hand hanging over the bed on the same side being decidedly swollen.

May 28th. For two or three weeks previous to this date there had been some improvement as regards the general condition, the patient sitting up occasionally, but the paralysis of the extensors remained complete. The following extract is from the ward notes of May 28th:

Watery diarrhœa continues; œdema of face and hands has entirely disappeared. The skin of the entire surface of the body has grown darker, with many brown patches, like freckles upon its surface, most marked on the hands and arms.

June 5th. This morning the patient is very weak, and since the disappearance of the œdema (which began to subside about ten days before this date) her emaciation is apparent. Her color is no longer typical of pernicious anæmia; skin is rather of a light-bronze tint; foot-drop still persists, although there is a little more power in its extensor tendons; hands much improved as to movements of extension.

On June 1st this patient passed out of my care, but from the notes it appears that the asthenia was rapidly progressive, and enhanced by rapidly recurring attacks of gastro-intestinal disorder. As above stated, death occurred on June 23, 1897.

The urine was repeatedly examined. On one occasion a trace of albumin was found, and on another a few small granular casts. Its specific gravity varied from 1014 to 1020.

A differential count of the leucocytes was recently made from a specimen of blood from this case by Dr. L. N. Boston, with the following result:

Polynuclear leucocytes	57	per cent.
Large lymphocytes	18	"
Small lymphocytes	20.5	"
Eosinophile cells	4 5	"

In counting 600 white cells 9 megaloblasts and 15 normoblasts were seen.

The following conditions were found at the autopsy:

Interstitial nephritis, ovarian cyst, multiple uterine fibroid tumors, atheroma of aorta, pericarditis in patches, vegetations in mitral valves, œdema of lungs.

Case II. *Profound anœmia following repeated epistaxis; characters of the blood as regards number of red corpuscles and percentage of Hb. the same as those of pernicious anœmia; convulsions following transfusion, the giver of the blood being epileptic; continued fever. Death.*—Samuel B., aged seventy years, colored, sent to the Philadelphia Hospital from the House of Correction, February 10, 1897. No history of previous illness except rheumatism until two months ago, when after a blow on the nose epistaxis began. This has continued at intervals ever since.

On admission the patient was in a semi-comatose condition. The tongue was thickly coated, the breath offensive, the bowels loose, and the ocular conjunctiva yellow. A soft systolic murmur was heard over the base of the heart, and a few mucous râles at bases of lungs behind; the respirations were feeble and the heart-sounds distant and muffled. Temperature the morning after admission 102°; pulse 100, soft and compressible; respiration 20.

The first blood count was made February 21st. Number of red cells per c.mm., 1,357,000; number of white cells per c.mm., 5236. The Hb. was not estimated, nor is there any record of a differential count of the white cells.

It should have been stated that epistaxis was present on admission, and was arrested by tamponing the nares.

The condition of the patient steadily deteriorated until March 5th, when I determined to employ transfusion after the method of Brakenridge, of Edinburgh. This consists of the intravenous injection of blood kept fluid by admixture of one-third of its bulk of a 5 per cent. solution of sodium phosphate.

The marked success attendant upon this measure, reported by Brakenridge and Affleck fully warrants its employment in cases of pernicious anæmia which do not improve under purely medicinal treatment. The entire amount transfused by Brakenridge at one time, or rather by Duncan, who performed the operations, varied from two to six ounces.

The operation was performed by one of my surgical colleagues, Dr. John B. Shober, on March 5th. Six ounces of blood were obtained from a colored man, an epileptic, of about the same age as Samuel B., the patient. The blood was immediately mingled with two ounces of a 6 per cent. solution of sodium phosphate and the mixture injected into the cephalic vein of the right arm under all the usual antiseptic precautions.

During the operation the patient became very restless, with marked dyspnœa, and perspired profusely. About two hours after the operation his nose began to bleed, and also the wound in the bend of the arm where the transfusion was made.

March 6th. Passed a bad night; pulse frequent and feeble, beating at the rate of 140 most of the time. The temperature, which at the time of the transfusion and for weeks previously had reached 102° in the evening, rapidly fell until, at eleven P.M. of the 6th, it reached 96°. After that it rose as rapidly until the evening of the 8th it reached 102 8°. It then resumed its former course until the patient's death on April 16, 1897.

The general condition of the patient began to improve on the 10th of March, up to which time he had been in a semi-comatose condition, with muttering delirium, feeble, rapid pulse, and almost inaudible heart-sounds. The treatment during this period consisted largely of the hypodermatic administration of strychnine in doses of one-twentieth of a grain.

15th. Had a good night and was bright and cheerful in the morning. During the day he had three convulsions, each lasting but a few seconds and attended with unconsciousness. The spasm was limited to the muscles of the face, which was drawn toward the right side. On the 17th he bit his tongue during one of these spasms, which still remained limited to the right facial muscles. After this date the convulsions did not recur. Those convulsive attacks excited considerable comment on the part of those who were familiar with the case, on account of the remarkable coincidence, if it is nothing more, that the giver of the blood transfused into the veins of the patient was an epileptic.

31st. The blood was examined to-day with the following result: Red corpuscles, 660,000 per c.mm.; hæmoglobin, 17 per cent.; white cells, 3600 per c.mm.

Death occurred on April 16, 1897.

An autopsy was performed, of which the following notes were made: Tuberculosis (?) of mesentery and retroperitoneal glands. Emphysema of left lung. Effusion into both pleural sacs and into the pericardium.

Old pleural adhesions in right side. Chronic interstitial nephritis. Splenization of bone-marrow.

Exception may be taken to my regarding this case as one of pernicious anæmia, on the ground that the illness began with, and was kept up by, loss of blood. The characters of the blood were, however, those of pernicious, not those of post-hemorrhagic anæmia. This is especially shown by the figures of the last count, which gave 13 per cent. of red cells and 17 per cent. of hæmoglobin.

In post-hemorrhagic anæmia the percentage of hæmoglobin is, as a rule, decidedly lower than that of the red cells,[1] and, in addition, there is not only a relative but an absolute hyperleucocytosis. In the case of Samuel B. the number of the white cells was absolutely diminished. The splenization of the marrow of the long bones is also corroborative of the diagnosis of pernicious anæmia.

A differential count of the blood cells recently made by Dr. L. N. Boston gave the following result:

Polynuclear leucocytes	48 per cent.
Large lymphocytes	37 "
Small lymphocytes	12 "
Eosinophile cells	3 "

In counting, 600 white cells, 3 megaloblasts, and 7 normoblasts were seen.

CASE III. *Extreme anæmia, with percentage of color higher than that of number; marked gastro-intestinal disorder; great improvement under the use of arsenic and orexine.*—Andrew F., aged forty-two years; laborer; admitted January 23, 1898.

Family history good, both parents living to advanced age, one dying at eighty-five, the other at seventy-two. One brother died from accident, another still living; a sister died from typhoid fever.

Up to April, 1897, the only illness of any moment experienced by the patient was typhoid fever, with which he was attacked when twelve years old. In April last he had an attack similar to the present one, characterized subjectively by great prostration and dizziness, and objectively by extreme pallor.

The present illness began four weeks ago at Sparrow Point, near Baltimore. The first symptoms were chilly sensations, lasting more than a week, followed by painful throbbing of the head. Two weeks before the chills began it was noticed that he was becoming extremely pale. The appetite has been very poor, the bowels regular, and there has been cough with slight expectoration.

On admission he appeared much older than his age—forty-two years. His pallor was extreme, and the mucous membranes milky white. Vessels at base of neck pulsated strongly. Pulse frequent, quick, and soft.

Lungs yield normal signs except in right infra-clavicular region, which is slightly dull, and over which there is slightly increased vocal

[1] See chart in "Die Anæmie," by Lazarus, in Nothnagel's Specielle Pathologie und Therapie.

resonance. Apex beat of heart not visible, but palpable in fifth intercostal space in nipple line. Soft, blowing, systolic murmur at apex. Liver not enlarged. Area of splenic dulness slightly increased. Deep reflexes very slight. Digestion much disturbed; anorexia marked; vomiting induced by slight exertion, such as getting out of bed.

Eye-ground examined by Dr. Charles A. Oliver, February 3, 1898: "Well-marked neuro retinitis with both deep-seated and superficial hemorrhages in retina and optic nerve, most marked in right eye."

The urine was examined on several occasions and found free from albumin and sugar.

The blood was examined on January 25th, two days after admission:

Number of red corpuscles, 884,000 = 17.6 per cent.; hæmoglobin, 25 per cent.; white cells, 8500. Marked poikilocytosis.

January 31, 1898. Second blood count:

Number of red corpuscles, 792,000; white cells, 8620

March 18*th*. Number of red corpuscles, 2,520,000 = 50 per cent.; hæmoglobin, 65 per cent.; white cells, 2986.

At one of the blood examinations a stained specimen showed nucleated red cells with karyokinetic figures.

During the first three weeks of this patient's stay in the hospital no improvement was manifest. His appetite continued very poor and his stomach very irritable, with daily vomiting. Up to this time he had been taking Fowler's solution in gradually increasing doses up to ten minims. He was now given orexine (gr. ij t. i. d.), and coincidently with its administration the appetite and digestion began to improve, and soon became almost voracious. On February 23d, it is recorded in the ward notes, he ate for his dinner four small chops, two potatoes, one egg, three slices of bread and a glass of milk. The increase in appetite may have been a mere coincidence, for I have since given orexine in cases of pernicious anæmia without any apparent influence upon the appetite.

The patient was discharged on April 7th, greatly improved, and, according to his own account, as well as he had been for years. His blood corpuscles, however, at the time, numbered less than 3,000,000 per c.mm.

With reference to this last point, *i. e.*, a state of well-being with 50 or 60 per cent. of the normal number of red cells, it would seem that in some cases of pernicious anæmia the possible maximum blood count is a low one. I have seen several cases in which patients with about 2,500,000 red corpuscles per c.mm. (*i. e.*, 50 per cent. of what is considered normal) declared themselves perfectly well and presented all the external signs of health. In one of the cases of this kind the patient, a man of high intelligence, being discouraged by the reports of the blood examinations, and finding himself in excellent condition, refused to have them continued, although he persisted in the use of the therapeutic measures from which he had derived so much benefit.

CASE IV. *Under observation six years, during which there have been several slight and two severe relapses, chronic gastro intestinal catarrh, with marked exacerbations preceding and during the relapses; complete restoration to health.*—W. P. O., aged fifty six years, male. This patient, an active and prosperous business man, a contractor, has been

under my observation since February, 1894, when I first saw him in consultation with Dr. L D. Judd. At that time his anæmia was extreme, and his general condition apparently hopeless. In the course of a few months his health was completely restored; in fact, his general condition became better than ever before. During the last six years he has had several slight and two severe relapses, the latter in the spring of 1898 and the autumn of 1899 respectively.

The clinical history is taken almost verbatim from notes furnished me by the patient himself: "February 19, 1894. Complying with your request I will endeavor to repeat in writing the verbal report which I gave you on the occasion of your first visit. I was afflicted with a severe spell of the grip the first year of its appearance here (1889–90), coupled with a stubborn bronchial cold, and, although I became quite strong again and active, I have always since felt that I did not entirely recover from its effects. The latter part of July, 1892, I had some very important work to do in a very limited time at ——— (in the neighborhood of Philadelphia), and spent at least three hours there each day, anxious in mind and tired in body. I accomplished the work a little ahead of time, but it resulted in, or at least ended with, a severe and protracted spell of diarrhœa. I had been subject to similar but shorter attacks for several years. After completing the work referred to, the entire business was thrown upon me for about two weeks, during which the diarrhœa continued. I was relieved on August 19th, and sailed for Boston, hoping to recuperate on the New England coast. The sea trip was very hot, and I suffered severely. I returned the next day, took to bed and remained there for at least two months, being unable to take nourishment without experiencing great distress. Toward the first of the year, 1893, I was able to get down town for a short time each day, but did not improve satisfactorily. Early in February I contracted a cold which resulted in an attack of erysipelas that lasted about two weeks. My convalescence was rapid; the condition of my stomach improved, and I was able to take cod-liver oil. Under its use I gained in flesh until in the spring of that year I weighed 138 pounds, about eight pounds more than I had weighed for a number of years. During six weeks of the summer of 1893 I was at Canandaigua Lake, but owing possibly to indiscretions in diet the diarrhœa returned and my health again became worse. It was still further impaired by the fatigue incident to a visit to the Chicago Exposition. During the fall my health and strength steadily deteriorated until I reached the condition in which you found me in February, 1894."

When I first saw this man, on February 3, 1894, he was ghastly pale, gaunt and emaciated; in short, presented the appearance of an advanced case of pernicious anæmia. The diagnosis was confirmed by the negative results of a thorough physical examination and by an examination of the blood:

Number of red corpuscles per c. mm., 1,237,500; poikilocytosis marked; numerous microcytes; hæmoglobin, 30 per cent.; white cells not increased in number. At this time he weighed 118 pounds.

His symptoms at this time, apart from the sense of great muscular weakness and dyspnœa on slight exertion, were those of gastro-intestinal disorder. There was great uneasiness after eating, borborygmi, gaseous eructations and abdominal distention. The urine at this time was free from albumin and casts.

The treatment instituted on February 3d consisted of five grains of naphthalin in capsules thrice daily before meals, and three drops of Fowler's solution immediately after meals. He had a good appetite and was prone to over-indulge it. The diet was, therefore, carefully regulated and restricted. It was composed of chicken, fish, chops and eggs, rice, mashed or baked potatoes, and boiled or roasted onions, of which he was very fond. He was also allowed farinaceous food in the form of mush, hominy, and oatmeal.

The dose of the Fowler's solution was gradually increased until on February 22d he was taking eight drops thrice daily. Calomel in fractional grain doses was also given at frequent intervals to regulate the bowels. A few days after the naphthalin was ordered he complained of the after taste of the drug, and bismuth salicylate in five-grain doses thrice daily was substituted. These substances were ordered with a view to intestinal antisepsis. He also took two drachms of cod-liver oil twice daily.

On February 22d he weighed 128 pounds, a gain of ten pounds in less than three weeks.

March 12, 1894. Number of red corpuscles, 2,762,500 (55.2 per cent.); hæmoglobin, 50 per cent.; poikilocytosis still marked.

Patient has just returned from a week's stay at Atlantic City, and looks and feels much stronger. Dispenses with his carriage in going to business, preferring the cars. Complains of slight looseness of the bowels. He has been taking ten grains of Fowler's solution thrice daily for the last two weeks. This was ordered to be stopped. Is to continue with the bismuth salicylate, which he has also been taking steadily.

April 2, 1894. Number of red corpuscles, 4,000,000; corpuscles still slightly irregular in size and shape, some of them "tailed;" hæmoglobin, 60 per cent.

It is interesting to observe, as I have pointed out in other cases, how, as improvement progresses, the blood, as far as the relative percentages of color and number are concerned, assumes the character of chlorosis.

23*d*. The patient had just returned from a few days' trout fishing in Monroe County, Pa., and looked the picture of health. In spite of constant out-door exercise, he had gained four pounds in weight. Number of red corpuscles per c.mm., 4,275,000; hæmoglobin, 70 per cent. Corpuscles much more regular in outline; white cells not estimated, but very scarce.

June 1. Weight 143 pounds, ten pounds more than at any time during the last ten years. Number of red corpuscles, 4,450,000 = 89 per cent.; hæmoglobin, 80 per cent.

In the meantime the treatment previously mentioned had been continued, with occasional intermissions, under the skilful management of Dr. L. D. Judd. The improvement continued during the summer and autumn of 1894, his weight increasing to 145 pounds in summer. No further examinations of the blood were made until February 18, 1895, when I was again consulted. For a few weeks preceding this date the digestive disorders have recurred and the patient's weight has diminished to 132 pounds. The bowels are irregular, constipation alternating with loose motions, and occasionally a mass of mucus is voided *per rec-*

tum. There is no external evidence of anæmia beyond a slight sallowness of the skin. Number of red corpuscles, 3,130,500 = 62 per cent.; hæmoglobin, 50 per cent. Corpuscles vary greatly in size and shape; no white cells seen while counting the red.

May 23, 1895. Patient has just recovered from an attack of erysipelas. Is very thin, weighing but 120 pounds. Number of red corpuscles, 3,970,000 = 79 per cent.; hæmoglobin, 65 per cent.

September 14. Mr. O. has been in the Pocono Mountains all summer, and is in good condition, having regained his lost weight. The blood was examined at his request. Number of red corpuscles, 3,550,000=71 per cent.; hæmoglobin, 55 per cent. He was surprised at the low figures, which, he said, did not correspond to his sensations. I was rather averse to examining the blood for fear of just such a result.

I did not again see Mr. O. professionally until May, 1898, but was informed that during this long interval he was in good health and actively engaged in business.

May 19, 1898. It is evident that he is suffering from a severe relapse. The skin is of a lemon tint, the lips and palpebral conjunctiva bloodless. Number of red corpuscles per c.mm., 1,800,000 = 36 per cent.; hæmoglobin, 38 per cent. No white cells seen in fields counted, or, in fact, in the entire specimen of diluted blood beneath the microscope. From this relapse he recovered completely.

Another decided relapse occurred during the autumn of 1899. He had been in the city all summer, and hard at work all the time at his office.

October 10, 1899. Number of red corpuscles per c.mm., 1,930,000 (38 per cent.); hæmoglobin, 35 per cent. Under the use of arsenic, intestinal antiseptics, and occasional doses of calomel, with a careful regulation of the diet, improvement soon set in, and in a few weeks he was able to walk a short distance and to take long drives. His blood was not again examined until January 20, 1900, when he came to see me. He looked remarkably well, had resumed his business, and declared that he was, so far as his sensations were concerned, in excellent health. His red corpuscles, however, numbered but 2,700,000 per c.mm., and the hæmoglobin amounted to 50 per cent.

I have made no further examinations of the blood in this case, but I have recently seen the patient, who considers himself in the best of health, and whose general appearance is indicative of vigor and activity.

On three occasions during the last six years I have seen this man apparently rescued from death by the treatment above outlined, and especially by the use of arsenic in doses pushed to the point of tolerance. I need scarcely remind anyone that we are indebted to Prof. Byrom Bramwell, of Edinburgh, for our knowledge of the value of this drug in cases of pernicious anæmia.

Case V. *Extreme anæmia of less than one year's duration; pleuritic effusion of left side; death from erysipelas.*—William T., aged sixty-two years, white, born in England, by occupation a wireworker; admitted to the Philadelphia Hospital January 25, 1900.

No disease since age of eighteen, when he had typhoid fever. Ten months before admission noticed that in the evening his feet and legs were swollen. Two months later he became decidedly short of breath,

and this dyspnœa has been increasing ever since. There is no pain, the appetite is fair, there are no marked digestive disturbances, and the patient sleeps well at night. For many years the man was a heavy drinker, but for the past year or two has refrained from the use of alcoholic liquors. He is of large frame and well covered with adipose tissue, but ghastly pale, the skin possessing the peculiar lemon tint of pernicious anæmia. Physical examination yielded negative results, except as regards the thorax, which on the left side was flat from the third rib downward in front, and below the spine of the scapula behind. Over this area, behind, the breath-sound was distant and bronchial, and the vocal and tactile fremitus completely absent. Two examinations of the blood were made in this case.

January 27. Number of red corpuscles per c.mm., 1,000,000 (20 per cent.); Hb., 20 per cent.

February 1*st*. Number of red corpuscles per c.mm. (average of two counts), 945,000 (19 per cent.); Hb., 18 per cent.

The corpuscles are irregular in shape, and their average size appears larger than normal. A few nucleated red cells (normoblasts) with deeply staining nuclei observed.

An ophthalmoscopic examination by Dr. Charles A. Oliver revealed "no coarse changes in either eye."

On February 16th the patient, who had been placed upon the use of arsenic, intestinal antiseptics, and orexine, and who was thought to be slightly improving, developed erysipelas, which involved the face and neck, and terminated fatally three days later.

An autopsy was held, of which the following notes are recorded:

"Body well-nourished; extremely anæmic; feet, legs, and thighs œdematous; abdomen containing 7000 c.c. of straw-colored fluid; left pleura contains 2000 c.c. of amber-colored fluid; entire pleura covered with a thick, well organized membrane; right pleura normal; heart cavities filled with liquid blood; no coagulum anywhere; valves and openings normal; coronaries slightly thickened; heart muscle shows increase of fibroid tissue; left lung is consolidated (from compression) and airless throughout; right lung emphysematous, with small scar at apex; liver pale, its capsule thickened, in a state of fatty infiltration, with slight increase of connective tissue; stomach normal as to size and thickness of walls; a few hemorrhagic spots on its mucous membrane."

The foregoing cases are selected from a number which have come under my observation during the last five or six years, because each of them possesses points of practical interest.

In Case I. there was paralysis of the extensors of the hands and feet, evidently due to peripheral neuritis. Whether this neuritis was toxic, induced by arsenic, or not, is an open question. It seems to me, however, that if such were the case peripheral neuritis would be of common occurrence in pernicious anæmia, most cases of which are treated with large doses of this drug. In one of the latest monographs[1] on pernicious anæmia it is stated that there are no symptoms of importance referable to the peripheral nerves.

[1] Die Anæmie, by Dr. A. Lazarus, ii. Abtheilung, s. 137.

In the same case there was bronzing of the skin, which might have been caused by the arsenic exhibited, and in addition there were freckle-like spots scattered over the surface of the integument. In another case, an old man under my care at the Philadelphia Hospital a few years ago, the entire surface of the body was covered with spots precisely resembling freckles, but the skin was not bronzed.

In Case II. the occurrence of convulsions after transfusion with blood from an epileptic has been already alluded to. If these convulsions had occurred immediately after the operation of transfusion they might have been reasonably attributed to the circulatory disturbance to which it gave rise. As, however, they did not take place until ten days after the transfusion, the coincidence of convulsions in the giver and receiver of the blood seems to me to possess remarkable interest.

In Case III. improvement coincided with return of appetite, which seemed to be excited and maintained by orexine. It is only proper to add, however, that I have employed orexine to stimulate the appetite in other cases, and in vain.

Case IV. is remarkable for the success attendant upon the treatment pursued, and illustrates also the notorious tendency of pernicious anæmia to relapse.

Case V., which terminated fatally less than a month after admission, is added, not so much on account of its being a well-marked case of pernicious anæmia as because it illustrates, as does also Case IV., the tendency of the disease to be complicated with erysipelas.

In all five of the cases the blood presented the characters which are universally accepted as those of pernicious anæmia, namely, extreme reduction in the number of the red corpuscles and relatively high percentage of hæmoglobin. All other blood changes in this disease, such as poikilocytosis, microcytosis, and the presence of nucleated red cells, large and small, are, from the practical stand-point of diagnosis, of subordinate importance. According to my experience there is no disease, except pernicious anæmia, in which the number of the red corpuscles is at any time reduced below 20 per cent. of the normal—*i. e.*, below 1,000,000 per c.mm. The disease with which pernicious anæmia is most apt to be confounded is, undoubtedly, latent gastric cancer. Marked digestive disturbances, extreme cachexia, and sometimes great emaciation are common to both, but the state of the blood, as regards the number of the red corpuscles, is widely different in these two affections. As I have said elsewhere,[1] I have never seen a case of gastric cancer in which the number of the red corpuscles was reduced below 30 per cent.—*i. e.*, below 1,500,000 per c.mm., and I have found in the blood of such a case a few days before death 2,760,000 red corpuscles

[1] Archiv für Verdauungskrankheiten, Band iv., Heft 1.

per c.mm.—*i. e.*, 45 per cent. of the normal number, while the percentage of color was but 20. In another case of advanced gastric carcinoma I found 60 per cent. of red corpuscles and 55 per cent. of hæmoglobin; in still another, 80 per cent. of red corpuscles, and so on. Such figures, in my experience, absolutely exclude pernicious anæmia. I have had under my care at the same time, in the same hospital ward, two cases—the one suffering from pernicious anæmia, the other from gastric cancer. The latter was far weaker than the former, while his red corpuscles were four or five times more numerous. In cancer of the stomach the oligocythæmia does not keep pace with the cachexia; in pernicious anæmia the cachexia does not keep pace with the oligocythæmia. In this connection I would call attention to the fact that the muscular strength and the powers of endurance are often remarkably well preserved in advanced cases of pernicious anæmia. For example, in the notes of a case which I reported in collaboration with Prof. Osler in 1886,[1] it is recorded that the patient "came to have his blood examined, walking a distance of nearly two miles. Was not fatigued, but complained of a slight numbness in the legs." At that time the red corpuscles numbered 1,215,000 per c.mm. (24 per cent.), and the percentage of hæmoglobin was 28. A similar case is recorded by Laache, the patient walking three kilometres, the entire distance being *up hill*, when his blood contained less than 1,000,000 red corpuscles per c.mm.[2]

To return to the question of the comparative number of the red corpuscles in gastric cancer and pernicious anæmia: In the former disease, when well advanced, in fact up to the point of death, I have found the number of the red corpuscles to range between 2,000,000 and 3,000,000 per c.mm., and sometimes to exceed the latter figure. On the other hand, I have never seen a case of pernicious anæmia in which, before death, the number of the red corpuscles did not fall far below 1,000,000 per c.mm. The comparatively high blood count of gastric cancer has been observed by others, and is, I presume, generally accepted as a characteristic of the disease. For example, Laache found 3,489,200 red corpuscles per c.mm. (about 70 per cent.) in a case of cancer of the stomach and liver less than two months before death;[3] 67 per cent. in another; 43 per cent. in a third, and 57 per cent. in a fourth. Similar figures have been published by Stengel,[4] who found an average hæmic unit of 58 in three advanced cases of gastric carcinoma. Contrast these percentages with 7, 10, and 18, which are those I have frequently found in advanced cases of pernicious anæmia. It is my opinion, as the result

[1] American Journal of the Medical Sciences, April, 1886.
[2] Die Anämie, S. Laache, 1883, p. 147. [3] Loc. cit., p. 63.
[4] Therapeutic Gazette, June, 1894.

of many years' observation, that the differential diagnosis between pernicious anæmia and latent gastric cancer, and consequently the diagnosis of these two diseases, may be more certainly made by a blood-count than by any other method, not excluding a chemical examination of the gastric contents. In fact, the latter may be misleading, as, for example, in cases of pernicious anæmia associated with extensive atrophy of the gastric mucosa. In such cases anacidity, which is a characteristic of gastric cancer, is present, as a matter of course. In the case already referred to, which was reported by Prof. Osler and myself, there was total destruction of the mucous membrane of the stomach. If in that case the stomach contents had been tested for HCl, the result would of necessity have been negative, and, therefore, misleading. The case was studied in 1886, before the importance of anacidity as a symptom of gastric cancer was generally recognized, and, therefore, the diagnosis was based upon the most reliable sign of pernicious anæmia, the reduction of the number of the red corpuscles to about 25 per cent. of the normal.

I admit the possibility of the reduction of the number of the red corpuscles in gastric cancer to 40 or even to 30 per cent. of the normal—*i. e.*, to figures characteristic of pernicious anæmia, although I have never met with such a condition. Supposing such a case to exist, I would regard it as one of pernicious anæmia complicated with gastric cancer, or as one of gastric cancer complicated with pernicious anæmia, for the figures last mentioned are characteristic of pernicious anæmia and not of gastric cancer.

The relatively high percentage of hæmoglobin, which is so characteristic of the blood of pernicious anæmia, depends upon two, perhaps upon three causes, of which but one is generally recognized: 1. It depends upon the increased average size of the red corpuscles, each one containing more than the normal amount of hæmoglobin. 2. Upon the fact that in some cases there is an unusual number of microcytes, which are so highly colored and so minute that they have been compared to "small, red-tinged, fat globules." They are much better seen in a dried smear of blood than in the diluted blood from which the count is made. Whether seen or not, they are not counted, and, therefore, contribute to raise the percentage of color. 3. A high percentage of hæmoglobin may depend upon the time at which the examination of the blood is made. Hunter has called attention to the fact that exacerbations of the disease coincide with an increased yellowness of the skin, sometimes amounting to icterus, and a deeper color of the urine, the latter being due to the presence of pathological urobilin, and all dependent upon increased hæmolysis. In other words, the icteric tinge of the skin and the deeper hue of the urine are hæmatogenous—*i. e.*, caused by a disso-

lution of the red blood-corpuscles. Now, if the hæmoglobin is estimated during one of these periods of exacerbation, its percentage will, as a matter of course, be higher than previously or subsequently, since the more highly-colored plasma contributes to its elevation. This is a point to which, as far as I am aware, attention has not hitherto been directed.

In conclusion, I would reiterate the theory announced by me in 1886,[1] and quoted with approval by the late Prof. Harrison Allen at the third Triennial Congress of American Physicians and Surgeons,[2] that the red blood corpuscles in pernicious anæmia show marked signs of reversion to the type of blood which is normal in the cold-blooded animals. This theory might be regarded as fanciful if it were based upon a resemblance of the blood of pernicious anæmia to that of the cold-blooded animals (frogs and eels) in any one particular, but the fact is that the red corpuscles of pernicious anæmia resemble those of the said animals in their number, their size, their shape, and the amount of hæmoglobin they carry. In well-marked cases of pernicious anæmia we observe (1) a reduction of the number of the red corpuscles to a degree that is normal in the cold-blooded animals. It is the rule to find in this disease, when well advanced, less than 1,000,000 corpuscles per c.mm. Figures like these are normal in the cold-blooded animals. (2) In pernicious anæmia many of the corpuscles are much increased in size, so much so that they have received the name of megalocytes. Many of them are quite as large as the corpuscles of the lizard and eel. (3) They often show a tendency to assume an oval outline, which is that of the corpuscles of the cold-blooded animals. And (4), finally, to make the resemblance complete, nucleated red corpuscles are commonly present in the blood of pernicious anæmia.

Dr. C. S. Engel,[3] of Berlin, has recently discussed the question whether pernicious anæmia is an example of reversion to the fœtal mode of blood development, and, after an elaborate and minute comparison of fœtal blood in all its stages with the blood of pernicious anæmia, he decides it in the affirmative. Such observations tend to support the view just advanced, for, according to all analogy, the blood-corpuscles of the human embryo in their various stages of development should correspond with those of adult animals on lower planes of evolution.

[1] Philadelphia Medical Times, April 3, 1886.

[2] Trans. of the Congress of Am. Phys. and Surg., vol. iii. p. 9. "Morphology as a Factor in the Study of Disease."

[3] Virchow's Archiv, Band cliii., S. 537.

PERNICIOUS ANÆMIA: A STUDY OF ONE HUNDRED AND TEN CASES.[1]

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The diagnosis in these cases rests upon the following evidence:

1.	Autopsy (in addition to clinical evidences) . . .	19 cases
2.	Typical symptoms, signs, blood examination, and course, ending in death—no autopsy . . .	60 "
	Typical symptoms, signs, blood examination, and course, but not known to be dead (lost sight of) .	19 "
3.	Typical symptoms, signs, blood examination, and course, but still alive (recent cases)	12 "
	Total	110 "

These figures will be further discussed later on, but are given here simply to indicate what is included in the paper. In addition to these 110 cases I have seen 22 others, which I think were probably cases of pernicious anæmia, but in which a full account of the histology of the blood or some other item necessary to diagnosis is lacking.

Etiology. Among my cases there has been a slight preponderance of males: 57 males to 53 females. The majority of the cases have occurred after the fortieth year; in fact, only 28 occurred at an earlier age. I have had no typical cases under nine years of age. I say no typical cases, for though I have known fatal cases of anæmia in younger children, the anæmia has always seemed to me to be of a different type from that occurring in older persons. Sixty-three of these cases occurred between the fortieth and the sixtieth year, 19 were over sixty, 4 over seventy, the oldest being seventy-nine.

All of these cases came from Boston or its vicinity, and almost all professions and walks of life were represented. One fact which surprised me was the occurrence of no less than seven cases in the wives of phyicians.

In four cases the symptoms began immediately after parturition or during the previous pregnancy. Of a relationship to the time of the menopause it is difficult to make any accurate statement, since the catamenia always stops when the anæmia begins. Fourteen cases occurred at about the time when the menopause is to be expected. No definite relationship with syphilis or with intestinal parasites could be traced in any case. There was a history of tertian malaria in four, but nothing pointed to its being the cause of the anæmia. Hemor-

[1] Read before the Association of American Physicians, Washington, D. C., May 1, 1900.

rhage played a part in the symptomatology of thirty-seven cases, but in no case preceded the onset of the other symptoms. The source of hemorrhage in these cases was as follows:

Bowel (including piles)	15
Nose	13
Gums (steady oozing in 2)	12
Stomach	7
Uterus	3
Lungs	2
Skin	2
Ear (1 pint lost on one occasion)	1
Kidney	2

Two cases were complicated by diffuse nephritis. There was no relation to cancer in any. Psychic factors were prominent in three cases. In one of these the patient's symptoms dated from the time when it was her misfortune to witness the suicide of her son.

FREQUENCY. The fact that so many cases came within my personal observation within seven years seems to me to show that the disease is more common than is usually supposed.

SYMPTOMS. On the whole, the most striking thing to me as I look over these cases is the uniformity and monotony of the symptomatology. One case is remarkably like another. Again, I am surprised at the relative freedom from symptoms in many of them. Several times I have had to restrain patients from going to work, although their red corpuscles numbered less than 2,000,000 per c.mm. Other patients with blood equally impoverished have told me that they felt almost if not quite well.

The gravity of such symptoms as are present does not seem to be in any way proportional to the impoverishment of the blood. Cases with only half a million corpuscles often feel better than others with a million and a half.

Again, it should be mentioned that pernicious anæmia is compatible with a very fair color in the cheeks. I have had three cases with typical signs and symptoms of pernicious anæmia in whom, from the appearance of the face, one would never have suspected the diagnosis.

The earliest as well as the most frequent of all symptoms is *muscular weakness*. In two cases this was the only complaint when the patient first came under observation. Next to this, the earliest as well as the most frequent complaint was of *pallor*, which in the great majority of cases had the pale yellow cast so often spoken of. This tint, while I do not think it can be held to be peculiar to pernicious anæmia, is certainly a very suggestive symptom; but it is rather the combination of yellow pallor with plumpness in the face which makes us suspect the presence of pernicious anæmia.

Next to these symptoms in the order of frequency is *dyspnœa*, then *gastric symptoms*—nausea or vomiting, which were nearly as common as those last mentioned. It is noteworthy that in fifty-seven cases the vomiting occurred without any antecedent nausea. In this series, as in that previously published,[1] I found it characteristic of the disease that gastric symptoms occur *paroxysmally*, with intervening periods of relatively good digestion. This fact speaks decidedly against the supposition that the changes in the gastric mucous membrane (which are present, no doubt, in many cases) are such as to cause a serious impediment to digestion or absorption. Atrophy of the gastric tubules cannot come and go as the symptoms do.

Lack of appetite was complained of in not more than two-thirds of the cases. One patient said he never could get enough to satisfy his appetite. Swelling of the lower extremities was a fairly constant although a relatively late symptom. Palpitation was complained of much less than dyspnœa. Physical examination of the heart showed in most cases nothing more than the functional murmurs which we expect in any anæmia. They are usually less marked in pernicious anæmia than in chlorosis. In seventeen cases there was evidence of mitral regurgitation, and in six of these cases an enlargement of the heart was demonstrated.

The condition of the *bowels* was abnormal in the majority of cases. Diarrhœa occurred paroxysmally in 43 cases and constipation in 32. Symptoms referable to the *nervous system* were as follows: Vertigo was complained of in about half the cases; headache in 34; ringing in the ears in 30; while signs and symptoms suggestive of changes in the spinal cord were present in 31. Difficulty of vision was mentioned in 20 cases.

Retinal examination was made in 36 cases. Of these 15 showed retinal hemorrhage; 21 showed a normal retina.

Enlargement of the *liver* could be demonstrated in 30 cases, and of the *spleen* in 13. About half the cases showed evidence of emaciation, while in the remainder the fat layer was well preserved. Fever occurred in about two-thirds of the cases, ranging from 100° upward in 23 cases; in 26 the temperature was constantly normal or subnormal. The urine was normal in 53 cases; showed the presence of albumin in 23 cases, with casts in addition in 21. It was usually pale or normal in color; only twice was it dark.

The Blood. There are undoubtedly periods in the course of most cases of pernicious anæmia in which the diagnosis cannot be made by the blood examination alone. The same can be said of malaria. But it is further true that the condition of the blood in a case of pernicious

[1] Boston Medical and Surgical Journal, 1896.

anæmia may vary a great deal from day to day, so that it is unsafe to draw conclusions from a single examination; for example, I have repeatedly failed to find any megaloblasts at the first examination, yet had no difficulty in discovering them a day or two later. Through reliance on the findings of a single examination I have twice made mistakes in diagnosis.

Regarding the characteristics of the blood in the active stages of the disease, I have nothing to add to what I have previously said in other writings;[1] but comparatively little has been written regarding *the condition of the blood during the remissions of the disease.* This I have had an opportunity of observing in many cases, and have noted the following facts:

1. The Color Index. When the red corpuscles begin to increase the color index may remain relatively high or even become still higher; but in the majority of cases this is not so. As a rule, in the remissions of the disease the hæmoglobin is relatively low, as in ordinary symptomatic anæmia, and I have seen two cases which, if examined for the first time during the period of remission, would have certainly been mistaken for ordinary chlorosis.

2. The Leucocytes. Coinciding with the increase in the red cells there is usually a still greater increase in the leucocytes, so that for a time a moderate leucocytosis may be present. This increase is made up very largely of polymorphonuclear neutrophiles, and is due, no doubt, to the increased activity of the marrow through which both red corpuscles and granular leucocytes are multiplied. As the percentage of polymorphonuclear neutrophiles increases the percentage of lymphocytes decreases, and the myelocytes, which are usually present in small percentages during the active stages of the disease, disappear. The number of megaloblasts steadily decreases, and in their place normoblasts appear for a time; later they, too, leave the circulating blood. The size of the individual red cells is sometimes greater during a remission of the disease than at any other time. In one remarkable case the patient, whose symptoms had totally disappeared and who was actively at work as a newspaper correspondent, dropped in to see me one day, apparently in splendid health and spirits. His skin and mucous membranes were ruddy red, his hæmoglobin 100 per cent., yet to my great surprise I found only 2,500,000 red cells to the cubic millimetre. The stained specimens showed the largest red cells which I have ever seen, for the most part perfectly well shaped and natural looking, but averaging 12 μ in diameter. This stage is, however, a comparatively short one, and the size of the red corpuscles soon becomes normal or subnormal. The abnormal staining reactions and the oval forms disappear.

[1] For summary of blood examination in 110 cases, see next page.

As a rule, the count of corpuscles does not remain long above 4,000,000, but ranges in the neighborhood of 3,000,000 during the greater part of the remission.

Summary of the conditions found in the blood of 110 cases at the time of the first examination:

a. Red cells numbered:

From 500,000 to 1,000,000 in	27
" 1,000,000 to 1,500,000 in	45
" 1,500,000 to 2,000,000 in	34
Total cases under 2,000,000	106
From 2,000,000 to 2,500,000 in	4
	110

b. Leucocytes numbered:

Under 1,000	9
1,000 to 3,000	23
3,000 to 5,000	40
5,000 to 7,000	24
7,000 to 10,000	12
10,000 to 13,000	2
	110

c. Hæmoglobin:

Relatively high in	79
Not relatively high in	31
	110

d. Average diameter of red cells at time of final examination:

Increased in	89
Not increased in	21
	110

e. Megaloblasts at time of final examination:

Predominate in	87
Later examination, predominate in	20
Only one examination, no megaloblasts	3
	110

f. Lymphocytes

between 20 per cent. and 30 per cent. in	34
" " 30 " " 40 "	34
" " 40 " " 60 "	33
" " 60 " " 80 "	6
" " 80 " " 90 "	3
	110

g. Eosinophiles:

Under 4 per cent.	90
Over 4 per cent.	13
None found	7
	110

h. Myelocytes. Present in 66 cases. Highest percentages:	
10 per cent. in	2
9 " "	1
8 " "	2
7 " "	2
	7

DIAGNOSIS. In view of the fact that there are but nineteen autopsies in my series, the question may be raised whether I have not included cases of latent gastric cancer or other disease, of which the anæmia was but a symptom. My reasons for thinking differently are as follows:

(*a*) In each of the nineteen cases in which an autopsy was obtained, the symptoms, the signs, the course of the disease, and the condition of the blood were of a definite and characteristic type, practically identical in every case, and differing in important respects from the conditions seen by me in any one of several hundred cases of well-identified symptomatic anæmia *of equal severity.*

(*b*) For purposes of comparison I have carefully studied the symptomatology, course, and the condition of the blood in several hundred cases of anæmia, obviously symptomatic, occurring in the course of æstivo-autumnal malaria, gastric cancer, or nephritis—all of them cases as severe as those included in my present series—that is, all of them showing less than 2,000,000 red cells per cubic millimetre. A very rich material for this study was furnished by the cases of malaria occurring in the soldiers returning from the late war in Cuba. Despite the most careful study of these cases, I have never been able to find any in which the symptoms, signs, course, and the condition of the blood were like those occurring in the nineteen cases of pernicious anæmia with autopsy, mentioned above.

The distinctive features in the diagnosis of pernicious anæmia are as follows:

1. A slow, insidious onset without recognizable cause.
2. Remarkable freedom from pain.
3. Striking absence of emaciation (in most cases).
4. The frequent presence of symptoms suggesting disease of the spinal cord.
5. Paroxysmal attacks of diarrhœa and vomiting, occurring without any obvious relation to diet or to treatment, preceded and followed by periods in which digestion and absorption were performed without apparent difficulty.
6. The tendency to great spontaneous improvement in all the symptoms, followed by rapid and inevitable relapse.
7. A reduction in the red corpuscles to a point below 2,000,000 per cubic millimetre, without a corresponding reduction in the hæmoglobin; a reduction in the number of leucocytes, and especially in the number

of polymorphonuclear neutrophiles; the presence of large numbers of oversized, well-stained red corpuscles, some of them containing nuclei (megaloblasts), together with a tendency to abnormal staining reactions and to an oval shape in the red corpuscles.

The distinctive features in the diagnosis of secondary or symptomatic anæmia are:

1. The presence of a well-recognized cause.
2. The steady progress of the symptoms, especially in malignant disease. If gastro-intestinal symptoms are present they seldom improve spontaneously.
3. Emaciation.
4. The blood.

This tissue shows usually a relatively low percentage of hæmoglobin, and the number of leucocytes, and especially of polymorphonuclear neutrophiles, is apt to be increased, although this is by no means invariable. The size of the individual red cells is usually normal or diminished and their centres strikingly pale. Oversized red corpuscles may be present and may occasionally contain nuclei; but, as a rule, they are greatly in the minority, and such nucleated red corpuscles as are present are chiefly of the normoblastic type. The tendency to abnormal staining reactions and to an oval shape in the red corpuscles is usually much less marked than in pernicious anæmia.

(*c*) Having established to my own satisfaction the existence of two types of anæmia—the one (pernicious anæmia) on the basis of nineteen autopsies and of a definite type of symptoms and signs occurring in every case; the other (secondary anæmia) recognized by the existence of an obvious cause, according to the action of which the symptoms progressed or ameliorated—it seems to me justifiable to conclude that the other cases of my series, which were clinically identical with the nineteen on which an autopsy was obtained, were cases of pernicious anæmia, and would have shown typical changes at autopsy, had this been obtainable.

Practically, latent gastric cancer with anæmia is the only disease which anyone is likely to confuse with pernicious anæmia. In all such cases which have come under my observation the symptomatology and course, as well as the condition of the blood, has been very different from that of typical pernicious anæmia. It is true that in two cases of typical pernicious anæmia, diagnosed as such by Ehrlich himself, a cancerous nodule the size of a walnut was found in the stomach post-mortem; but in such cases I see no sufficient reason for believing that the cancer was the cause of the anæmia. Cancerous growths are not usually accompanied by any considerable degree of anæmia until they have reached a considerable size. It seems to me more reasonable to suppose that in Ehrlich's cases the cancerous nodules occurred as a

complication and not as the cause of the anæmia. Latent cancerous growths complicating other diseases have been repeatedly found, and no one would consider a case of nephritis or of phthisis due to cancer of the stomach because such a growth was found in the stomach post-mortem.

(*d*) "*A priori* (Askanazy and other writers have said), there cannot be a distinction clinically between pernicious anæmia and secondary anæmia, because there is no distinction in the marrow between normoblast and megaloblast." This is not upheld, however, by later research. Pappenheim's work goes to show that there are two types of blood formation—the fœtal and the adult—with two types of corpuscles, differentiated, not, as Ehrlich supposes, by the fate of their nuclei, nor, as has often been stated, by the size and staining affinities of their nuclei, but chiefly by the size of the whole cell and by the characteristics of the nuclear network. It is practically though not strictly true to say that a megaloblast is an abnormally large red corpuscle with a nucleus of any kind, while a normoblast is a normal-sized red cell with any kind of nucleus. Large, pale nuclei are simply young nuclei.

(*e*) It is a common mistake to suppose that by pernicious anæmia we mean simply a very severe or fatal anæmia. But pernicious anæmia is not always very severe; there are relatively mild cases which run on for several years and are compatible with a very fair degree of health, although always fatal within six years, so far as my observation goes. On the other hand, a case of secondary or symptomatic anæmia, such as that due to hemorrhage or to malaria, may be rapidly fatal and yet is easily distinguishable from pernicious anæmia by its symptomatology and by the condition of the blood. I have no experience leading me to believe that there is any such condition as "secondary pernicious anæmia."

(*f*) In the initial stages of the disease and during remissions diagnosis may be impossible. The same is, of course, true of many of the best known diseases.

(*g*) The anæmia due to intestinal parasites, especially to the bothriocephalus latus, is entirely indistinguishable from pernicious anæmia. This has been abundantly proved by the magnificent monograph of Schumnn, and if we are to consider bothriocephalus anæmia as *secondary*, as it seems natural to do so, we must admit that this particular type of secondary anæmia is absolutely indistinguishable from the so-called primary or pernicious anæmia.

A word may here be said regarding the use of the term "primary anæmia," which means to me simply an anæmia of whose cause we are ignorant. None of the causes as yet adduced to explain pernicious anæmia seem to me satisfactory, although I think there is a good deal of evidence for believing that it is due to a poison absorbed from the

gastro-intestinal tract and exerting its deleterious effect upon the blood, the heart, the spinal cord, and the gastro-intestinal tract itself. Among these changes I am by no means sure that the anæmia is the most important, and I regard the others as co-ordinate with it rather than as resulting from it. This view is, to my mind, supported by the fact that the severity of the clinical symptoms is not by any means proportional to the degree of blood impoverishment.

Course. In 90 cases I have accurate data as to the course and progress of the disease; in the others my records are somewhat defective. Out of these 90 only 20 were progressive. In 70 there was one or more remissions in which great improvement took place, the symptoms for the most part disappearing, the patient's color and blood-count becoming nearly or quite normal. Twenty-one of these cases were able to return to work, and felt as well as ever.

Although it is well-known that pernicious anæmia is not a progressive disease, but comes upon the patient in successive waves or paroxysms, I think the full significance of these facts has not been realized. But a short time ago I was talking with a member of this Association, who seemed inclined to doubt the diagnosis of a case of pernicious anæmia because the improvement of the case had been so marked and so rapid. I desire, therefore, to emphasize the point that the disease rarely goes on progressively from bad to worse, and should be expected to show one or more waves of great improvement—improvement which for the most part occurs without any relation to treatment, and which treatment has no power to render permanent.

I have thought it of interest to put together the rate of improvement in some of my cases:

In Case VII. of my series the red cells increased from 1,800,000 up to 5,200,000 in fourteen days. In Case XXXIX. the red cells increased from 2,200,0000 to 4,000,00 in thirteen days. In Case LVIII. the red cells increased from 1,500,000 to 3,200,000 in twelve days. In Case XCI. the red cells increased from 1,700,000 to 3,000,000 in fourteen days.

Similar observations have been reported by Ehrlich and other observers.

It is quite possible, although I have no figures to prove it, that in the periods of decline the red corpuscles may fall as rapidly as they subsequently rise. This possibility is suggested by the fact that one rarely sees pernicious anæmia in an early stage—that is, until the red corpuscles have fallen below 2,000,000 per cubic millimetre. Only four of my cases showed more than 2,000,000 red corpuscles per cubic millimetre at the time of the first examination of the blood.

Prognosis. Of the seventy cases which I have been able to follow from start to finish the majority have lasted less than two years; only

twelve lasted more than three years, and only two more than four years, the longest being five years. The number of relapses varied from two to five or six. It has seemed to me that such relapses were especially apt to occur in the early spring, and I think it not impossible that a more direct relationship between the progress of the cases and the weather may later be demonstrable. Remissions may occur even after the red cells have fallen as low as a half million per cubic millimetre. In one of my cases the patient went steadily down hill for four months, until he was too weak to leave his bed, and finally became comatose, with convulsions. At this time he was not expected to live through the night, yet he subsequently recovered sufficiently to be able to do light work about his farm. In the active stages of the disease continuous fever may be present, and in two such cases the diagnosis of typhoid was made.

Out of the whole series there has not been one genuine recovery, so far as I am aware. Of the twelve who are known to be still alive eight have been under observation only a few months, and are fast going down hill. Of the other four, two have been under observation for two years, one for two and a half, and one for three and a half years. In the latter case the condition of the blood is now entirely normal, except for a moderate diminution in the hæmoglobin. The patient feels entirely well.

Of the nineteen whom I have lost sight of the majority were getting rapidly worse when last heard from.

Duration. Of the seventy-nine cases regarding which I have complete data, including the date of death—

30	lived	less	than	1	year	from the earliest symptoms.	
20	"	"	"	2	years	"	"	"
10	"	from	2	to	3	"		
7	"	"	3	to	4	"		
3	"	"	4	to	5	"		

Treatment. Most of these cases received Fowler's solution in gradually increasing doses continued over long periods. In eight of them bone-marrow was used, either alone or with Fowler's solution. In three of them inhalations of oxygen were given. Personally I do not believe that any of these therapeutic agents have any effect on the course of the disease. I have seen great improvement follow each of them, but when the inevitable relapse later took place the use of the same remedies proved unavailing. On the other hand, I have several times seen sudden improvement occur and the blood-count become normal when absolutely no medicine was being given. Several times such improvement followed immediately upon or coincided with an attack of diarrhœa, as if the increased intestinal peristalsis had removed from the system substances which were poisoning it. Acting upon this sugges-

tion, I have of late treated several cases with laxatives or purgatives, in the hope of preventing thereby the absorption of poisonous substances from the intestines. As to the results of such treatment I am not yet prepared to speak.

EXPERIMENTAL RESEARCH SHOWING THAT URIC ACID SECRETION IS NOT REGULARLY DIMINISHED IN THE PERIOD PRECEDING EPILEPTIC SEIZURES.

By James J. Putnam, M.D.,
of Boston, Mass.,
and
Franz Pfaff, M.D.,
of Boston, Mass.

The toxic theory of disease-processes, and especially of the periodical and occasional neuroses and psychoses, has so warmly commended itself to the minds of physicians of our generation, and has been utilized with such eagerness as a basis of therapeutics, that sufficient pause has not often been made to ascertain whether the data on which the clinical statements have been based would stand the searching test of really accurate and critical analysis.

For my own part, I believe that the point of view itself has often been wrong, and that, at least so far as the neuroses and psychoses are concerned, it may prove that the toxic theory of their pathogenesis should take a subordinate place, and that a more fruitful line of research would be one that looks on these affections as caricatures of normal states, their peculiarities being expressible, no doubt, in chemical terms, but better, it may turn out, in those of physiological reaction or anatomical structure.

This search for toxic causes has naturally been especially active with regard to epilepsy, and has been held by many observers as representing, indeed, the only rational outlook for an explanation of its symptoms, though of late the "inhibition" theory, as expressed, among others, by Oddi, the Italian physiologist, has been advanced as a promising alternative.

One of the most recent supporters of the toxic theory of epilepsy is Kräinsky, a Russian physician and chemist, who has made several long series of apparently painstaking experiments, the results of which are recorded in the *Zeitschrift für Psychiatrie*, 1898, and elsewhere. This paper opens with the very positive and reiterated statement, on which, indeed, the final reasoning and conclusions are based, that the excretion of uric acid is invariably diminished before each outbreak of "idiopathic" epilepsy, the diminution sometimes immediately pre-

ceding the attack, sometimes being separated from it by an interval of normal excretion for a day or two. Immediately after the seizures the uric acid excretion rises again, he says, to above the normal, so that the total excretion for the whole period equals the normal quantity. He does not agree with Haig in thinking this substance to be the direct cause of the attack, but regards the variations in its excretion as corresponding to other chemical changes, through which the real poison is formed. For him this poison is carbaminic acid, but into the soundness of this hypothesis we shall not here attempt to enter.

Having been interested for some time past, together with Dr. Pfaff, in studying the uric acid question, I asked him to test the validity of Kräinsky's statement as to the invariable diminution of the excretion above referred to, which, if proved to occur, would be a very important fact, as showing that the epileptic attack is led up to by changes in general metabolism.

The research does not cover a large number of cases, but so far as it goes it is accurate. Not only were the analyses made by an assistant especially trained for the work and under Dr. Pfaff's personal supervision, but control analyses were made in every instance, and all results rejected which were not thus confirmed, except in two instances.

The urines were sent to Dr. Pfaff daily from the Massachusetts State Hospital for Epileptics, at Monson, through the kindness of the Superintendents, Dr. Owen Copp and Dr. Everett P. Flood, to whom we express our sincere thanks.

The method of analysis followed was the Ludwig-Salkowski—the one now regarded as the best.

In all, twenty-nine specimens of twenty-four hours' urine were analyzed, coming from two patients. The first patient had five seizures during the period (three months) corresponding to the analyses; the second patient had two seizures during one month (October) and one seizure during another month (April). The results, as may be seen by examination of the accompanying table, cannot be said to bear out Kräinsky's categoric statements, either as regards the low excretion before the attacks or the high excretion after them.

In two instances the amount was very low, both on the seizure day and the day following, perhaps corresponding with the patient's presumably reduced state, or, indirectly, to a diminished ingestion of food. If there is any general conclusion to be drawn from the figures it is that the uric acid excretion of both patients was lower than that usually seen.

A reliable determination of the conditions of uric acid excretion taking place literally just before epileptic attacks must always be attended with difficulty, not so much because it is hard to anticipate the seizure as because the amount of excretion varies considerably for the different parts of the day and with the varying character of the food.

Patient.	Date.	Seizure.	Amount of urine.	Uric acid by first analysis.	Uric acid by control analysis.	Average.	Amount of uric acid in 24 hrs.
*[1] Case one	Oct. 22, 1899	Before	1370 c.c.	0.0641	0.0620	0.063	0.431
* " "	" 23, "	"	2810 "	0.0309	0.0288	0.029	0.419
* " "	" 24, "	Seizure	520 "	0.0618	0.0560	0.059	0.153
* " "	" 25, "	None	1670 "	0.0159	0.0121	0.014	0.116
* " "	Nov. 26, "	Seizure	2100 "	0.0313	0.0272	0.0293	0.307
* " "	" 27, "	None	1710 "	0.0532	0.0500	0.0516	0.441
* " "	" 28, "	"	530 "	0.1408	0.0270	0.0339	0.355
* " "	Dec. 2, "	"	1260 "	0.0992	0.0904	0.0948	0.597
* " "	" 3, "	"	2260 "	0.0432	0.0428	0.0430	0.486
* " "	" 4, "	"	1390 "	0.0382	0.0372	0.0377	0.262
* " "	" 5, "	Seizure	1100 "	0.0770	0.0740	0.0755	0.415
* " "	" 6, "	None	1870 "	0.0562	0.0527	0.0544	0.509
* " "	" 7, "	"	1290 "	0.0900	0.0820	0.0860	0.554
" "	" 18, "	Seizure	1170 "	0.015	0.011	0.013	0.120
" "	" 19, "	"	870 "	0.014	0.012	0.013	0.087
" "	" 20, "	None	1500 "	0.020 + (0.2016 g. precip. out) =			0.426
* Case two	Oct. 21, "	"	1260 "	0.0813	0.0795	0.0804	0.506
* " "	" 22, "	Seizure	900 "	0.1314	.....	0.1314	0.591
* " "	" 23, "	None	2120 "	0.0514	0.0540	0.0527	0.558
* " "	" 24, "	Seizure	1640 "	0.0749	0.0481	0.0615	0.504
* " "	" 25, "	None	680 "	0.1690	0.1804	0.1747	0.593
* " "	" 26, "	"	1260 "	0.0526	0.0446	0.0486	0.306
" "	Apr. 24, 1900	"	1275 "	0.0550	.....	0.0550	0.522
" "	" 25, "	"	1600 "	0.026	0.025	0.0255	0.30
" "	" 26, "	"	1110 "	0.037	0.033	0.035	0.28
" "	" 27, "	"	1060 "	0.030	0.029	0.0295	0.23
" "	" 28, "	"	1135 "	0.017	0.010	0.013	0.10
" "	" 29, "	Seizure	1150 "	0.022	0.019	0.025	0.17
" "	" 30, "	None	540 "	0.0081	0.0080	0.008	0.032

It seemed to us that the best way to begin, at all events, would be to examine a continuous series of twenty-four hour specimens, to ascertain whether uric acid excretion was different on seizure days from that on free days. We did, however, in one or more instances, examine antiparoxysmal specimens, but without finding such differences as encouraged to further pursuit of this method.

[1] All the analyses marked in the table by an asterisk (*) were done by the older method of analysis as given in Hoppe-Seyler's Handbuch der Chemischen Analyse, Berlin, 1893, p. 358.

All the analyses not so marked were done by the same method, with a slight modification, as given in Salkowski's Practicum der Physiol. u. Path. Chemie, 1893, p. 239.

MINOR FORMS OF CARDIAC DILATATION.[1]

By Beverley Robinson, M.D.,
of New York.

Cardiac dilatation in a pronounced degree, due either to organic valvular disease or to obvious myocarditis—acute or chronic—is no doubt recognized and properly treated by the average good and careful clinician. This affection in its minor degree is frequently confounded with some other ailment, or when recognized not given its due importance, and hence ignored so far as active, direct treatment is concerned. Cardiac dilatation when at all advanced may usually be recognized, as we know, by the usual methods of physical examination.

Percussion shows increased cardiac dulness, especially in a lateral direction; palpation finds the heart impulse lessened in force, more diffuse, and the locality of the apex-beat often somewhat changed, and not always readily determined. Inspection corroborates these findings more or less well. The use of the stethoscope in addition reveals feeble, irregular heart sounds. The two sounds of the heart resemble one another more nearly—the long pause is shortened. We may or may not have a soft blowing murmur at the apex of the heart, and this murmur, usually systolic, may also be diastolic. The pulse is rapid, irregular, depressible, as a rule. It may be very infrequent. Dyspnœa, palpitations, and occasional præcordial pain as symptoms of cardiac dilatation are not unusual. Now and then we have in most pronounced cases blueness of lips and fingers, obstructed general venous circulation, and œdema of the lower limbs. The foregoing is a brief picture of cardiac dilatation in its advanced stage.

As I meet it in minor forms in my daily rounds of practice it does not appear precisely after this manner, and I have been often misled as to its presence and significance. One very ordinary type is that of the anæmic girl just past the age of puberty. She suffers often from too profuse menstruation, constipated bowels, and gaseous eructations from the stomach; she has little or no appetite, and is constantly tired and nervous. The heart fluttering and irregularity (subjective) which go with these symptoms we recognize, and yet how seldom do we consider the heart action in these instances as being indicative of organic change, which must be treated properly and effectually if we are to obtain good, curative results. Such cases require iron and oxygen, rest and massage, proper diet and restricted hours of mental effort. They also require, still more, and in the beginning of treatment it is absolutely essential, small, repeated doses of digitalis and nux vomica until their hearts respond forcibly or at least with power sufficient to enable us to make

[1] Read before the Association of American Physicians, Washington, D. C., May 1, 1900.

satisfactory use of the other means to restore bodily activity. How shall we recognize such cases? Oftentimes with much difficulty, unless we appreciate rather obscure clinical facts. There is no diffuse or weakened cardiac impulse. On the contrary, the heart apex beats in the fifth interspace below and inside the nipple line. It may be of good force and not at all irregular. Abnormal sounds are not always present. There may not be any marked accentuation of the second sound. As a rule, however, the action of the heart is more frequent than normal, and the first sound is exaggerated, seemingly irritable. Give these patients for a week or two digitalis and strychnine in moderate doses, and follow them with a prolonged course of iron, and we get our best results. Act differently, and we are disappointed in our effort, time and again, to relieve symptoms and improve the general health.

One of the proofs, as I believe, which show the correctness of my diagnosis is that frequently in these cases the urine is light colored, of low specific gravity, containing neither albumin nor casts, and it may or may not be in sufficient quantity. Rest in bed will change this urine so far as color, density, quantity, and the elimination of urinary solids are concerned. It will also be effected and more rapidly sometimes with rest, sometimes without, by the use of suitable cardiac tonics in very moderate doses.

I know such a condition is often attributed to impairment of the nervous tone, or perhaps to hysteria. So, indeed, it is at times; but behind this frequently is the loss of a certain amount of cardiac muscular power. The cavities of the heart are doubtless slightly enlarged, and particularly that of the left ventricle, and the walls thinned. There is no hypertrophy, and why? Simply because there is not sufficient vital energy to produce it. The power of the heart can only be increased in one of two ways: by general corroborant treatment, or, at first, by suitable cardiac stimulation, and subsequently followed by the second. The latter plan is the speedier and better one, as I believe.

Formerly in some of these cases I was at times in reasonable doubt for a while as to whether I had to do with beginning renal changes of interstitial nephritis. The age of the patient, the anæmic state, and the rapid effects of judicious treatment settle all reasonable doubts very soon at the present time in the great majority of cases. In these instances is the heart muscle structurally affected? Is there granular or other degeneration of cardiac fibres? I do not believe so, at least in the great number of examples, in view of the success of treatment after several weeks or months. In other instances, where there little or no favorable response to rational medication, change of air and nursing, and where the examination of the blood by an expert shows signs that indicate a formidable anæmia feigning the pernicious form, I am convinced that we have to do with parenchymatous changes of the myocardium of more or less grave import.

Is there any method by which we can demonstrate these changes to the skeptical during life? Certainly not. All we can do is to reason from analogy and our pathological findings in more serious states which go on to a fatal termination. Fortunately, the overworked shopgirl, or the tired-out society young lady, when she gets the care required, ultimately, and as a rule, gets fairly well. I have no doubt in my own mind that in many instances perfected development or full growth of the body reached from the twentieth to the twenty-fifth year explains the happy termination of some cases. In other words, these cases in a measure may be self-limited. To the unconvinced listener who would call such cases merely functional, I would answer: if they are then the words of Sir Andrew Clark apropos of another topic seem to be singularly suggestive and true:

"We are," writes Clark, "so much concerned with anatomical changes; we have given so much time to their evolutions, differentiations, and relations; we are so much dominated by the idea that in dealing with them we are dealing with disease in itself, that we have overlooked the fundamental truth that these anatomical changes are but secondary and sometimes the least important expressions or manifestations of states which underly them. It is to these dynamic states that our thoughts and inquiries should be turned; they precede, underlie, and originate structural changes; they determine their character, course, and issues; in them is the secret of disease, and, if our control of it is ever to become greater and better, it is upon them that our experiments must be made."[1]

Another form to which I would direct attention is that of the somewhat obese woman—married or unmarried—between forty and fifty years of age. Not infrequently these women have a marked rheumatic tendency. Not infrequently their urine on cooling deposits an excess of urates or uric acid. They often have slight attacks of bronchitis, ambulatory neuralgic pains, localized dry pleurisy. When in their usual health they can take moderate exercise without great distress. So soon as they have any acute ailment or depletion they suffer from marked difficulty of breathing, a gone feeling at the epigastrium, and an inward sense of suffocation, as they express it. Usually their cardiac action is feeble, rapid, and slightly irregular under these circumstances. Physical examination may or may not reveal at this time a soft, blowing murmur—systolic as a rule, often heard with greatest intensity in the mitral area, but also heard at times in the left intercostal spaces above the nipple or at the lower end of the sternum. The blood may or may not show a moderate degree of anæmia. During and after their menstrual epochs these patients are often at their worst, and whenever their

[1] British Medical Journal, August 16, 1884, p. 312.

flow is abundant their condition inspires great solicitude. They do not always have fever when they have their slight bronchitic or pleuritic attacks. At other times the temperature rapidly goes to 102° or even higher, and areas of local pulmonary congestion are accurately made out. Such cases are amenable to judicious treatment, and in the course of ten days or two weeks very great temporary improvement will take place. I usually give very small repeated doses of nux vomica and strophanthus in the beginning of these attacks. I insist upon rest in bed and frequent small quantities of liquid or easily digested food. Where there are cough and local signs of dry pleuritis a small fly-blister, though painful, is a sovereign remedy. Of course, the menstrual flow when excessive should be controlled with ergot or hot douches.

In some of these cases where there is also well-marked anæmia there is present at times and in a more or less continuous manner a small amount of albumin in the urine. The clinical examination of the urine is such that I have known patients of this sort to be told that they were suffering from nephritis, and it was essential for them to live during a long period upon a milk diet, and to reside in an equable, dry, and relatively mild climate. In these cases the albumin would at times disappear, but fatigue, indiscretions of food, and temporary excitement would apparently bring back the albuminuria. I have no doubt the kidneys were affected with chronic congestion. I am also very confident that the hyperæmia was passive rather than active, and was, in reality and mainly under the dependence of a weak heart, quite insufficient in its action to keep up a proper vascular tension in the renal arteries. Here, again, judicious cardiac treatment was essential at first. With the digitalis or strophanthus, however, I usually combine a small quantity of nitroglycerin, as I deem it very important to dilate the peripheral circulation and thus lessen the work of the heart necessary to become effective.

There is another type of woman, and she is usually thin and nervous about the time of the climacteric or past it. The menstrual flow if it still exists is slight. These patients may not be anæmic to any appreciable extent. They have frequently very imperfect digestive assimilation. They may have some dilatation of the stomach, and are frequently nauseated and unable to take even the simplest forms of food for a time without causing great and rapid gaseous distention, not only of the stomach but also of the bowels. The liver is inactive and the bowels are torpid. We can give few medicines by the mouth except stomachics and carminatives without making their condition worse. Although their heart is extremely feeble, so much so at times in fact that we dread almost to move or raise them to make a proper exploration of the chest, yet if we so much as try to use any medication by the mouth to strengthen heart action we shall almost surely bring on worse

distress and perhaps excessive nausea and repeated vomiting. I have been obliged to treat such a patient for days at a time with digitalin and strychnine hypodermatically, while inhalations of oxygen were frequently administered. Rectal alimentation with panopepton, peptonized milk, egg, brandy, and a little opium at times took the place almost entirely of feeding by the mouth for several days. Where the repeated use of the hypodermatic syringe set up local irritation I was obliged to incorporate my cardiac stimulants with very small rectal enemata of water. Finally, after weeks of anxiety and constant nursing and unremitting attention, these women slowly regained their health and strength, and the heart became sufficiently strong to satisfy ordinary demands made upon it when the patient went about in a very limited measure. The urine never, upon repeated examinations, showed either albumin or sugar, but did show low specific gravity, deficient elimination of urea, and perhaps a few hyaline or granular casts. I could not positively affirm any general arteriofibrosis. I could and did strongly suspect its presence. The heart gave all the evidences of slight dilatation of the ventricular cavities, but at no time was there any manifest hypertrophy. In some patients there was rarely any cardiac murmur, and all I could detect, as a rule, was great feebleness of heart action without irregularity or intermissions. I have no doubt, for my part, that if these hearts were examined post-mortem they would show few or no changes other than those which follow. They would be soft and flabby. They would not retain their rounded, globular form, but would flatten on the table through partial collapse of the walls. There would be no valvular changes. The orifices might be slightly dilated. There would be, as stated already, slight enlargement of the cavities and thinning of the muscular walls. The color of the heart muscle would approximate that of the faded leaf; perhaps, usually it would only be relatively pale and bloodless. The cavities would contain small, imperfectly-formed post-mortem clots or liquid blood. Under the microscope we should find the striæ here and there imperfectly marked. There would possibly be some well-marked granular degeneration at times, and only very rarely the evidence of fatty degeneration. If the latter existed it would more likely be in patches in the capillary muscles, the septum, or the ventricular walls than generally diffused.

Unfortunately, these are at best clinical impressions rather than well-ascertained facts. And why? Simply because post-mortem examinations of these cases are not made. The patients do not die, in my experience, at least outside of hospitals. In hospitals, when they die, they have more advanced and graver phenomena of a similar condition; and then it is we can surely and positively affirm what our findings are.

In many instances I have had a report from the pathologist which in its main features was not unlike what I have attempted to describe.

In this connection I would refer to a paper of Dr. Danforth, of extreme interest to me, read at the last meeting of this Association, on "Clinical Forms of the Uric-acid Diathesis." It seems to me that some of Dr. Danforth's cases may have been mainly instances of cardiac dilatation in which the renal manifestations were merely a resultant of a weak, feeble heart action. At all events, I have portrayed the other side of a clinical picture frequently encountered by myself. I do not wish to convey the impression that I have made a new discovery—such cases as mine are met with by all of you. They are also described more or less perfectly in almost every text-book of cardiac disorders of the last fifty years. Still, I am free to confess that I do not know precisely where you will find the clinical picture I have endeavored to delineate in quite the same terms.

I may be asked whether I do not find these cases also among men. Perhaps I do, but I do not recall them in such a vivid manner as to be able to portray them. The laboring man, even though he may never suffer from actual valvular disease, will undoubtedly have at times marked cardiac dilatation. But usually there is more or less hypertrophy combined with it, and, even though the heart has become very incompetent through structural weakness, there will be such considerable enlargement that we feel confident that the autopsy will show more or less thickening of heart walls. The same is true of old valvular disease accompanied with cardiac enlargement. It is equally true, as a rule, where the history shows that there has been a persistent and excessive alcoholic habit. This is true also, although in less degree, of the business or professional man affected with heart disease.

Extreme cases of heart dilatation and no hypertrophy are also met with among men; but the minor degrees, those to which I have referred and tried to describe, are usually found among women. The intense heart failure, coming on rapidly, almost suddenly at times among men, and unquestionably due to very great cardiac dilatation, against which the heart is almost powerless to react, is sometimes seen after great excesses. These cases, as we all know, may be rapidly or suddenly fatal, despite our most active means of resuscitation. Among these cases, however, are unquestionably some in which the physical signs of cardiac dilatation are impossible to determine accurately. I can, therefore, well understand that their existence should be denied. In place of such a diagnosis I can but substitute one of loss of nerve-power, either in the intracardiac ganglia or in the trunks of the vagi. To admit this would be perhaps also to acknowledge that the heart muscle was intact and the cavities of normal dimensions. Such a belief would be strengthened by those instances in which certain cardiac tonics, and especially digitalis, are of little apparent value, perhaps, indeed, directly injurious,

and rest in bed and suitable liquid diet with alcoholic stimulants appear to be most useful.

Again, there are instances in which there is certainly no pronounced structural kidney change, where we watch closely the sequence of clinical phenomena. This is renal inadequacy only. The secretion of healthy urine, viz., of normal color, density, in sufficient quantity and without abnormal constituents, after a few days or weeks of rest, and when the patient is given easily assimilable food, returns, and our temporary fears are allayed. In some cases I recognize a possible spasmodic condition of the peripheral vessels and especially of the kidneys. We have intimation of this by high pulse tension at times and the rapid good effects of repeated small doses of nitroglycerin. Occasionally I have seen cases in which the heart action was very feeble, without any accentuation of the aortic second sound, and where the radial pulse itself had no increased tension, and yet nitroglycerin was of undoubted service, for after its use the heart's action was notably improved, and the secretion of urine, from being almost colorless and even small in quantity, took on its normal appearance and character. No doubt the nitroglycerin acted as a direct heart tonic to the cardiac muscle itself; no doubt, also, it dilated the small vessels of the kidney, breaking up any spasmodic condition that existed, and thus was of very great benefit to the patient. At all events, I have certainly seen nervousness, marked twitching of the muscles, apathy and somnolence—all symptoms, as I believe, indicating more or less so-called uræmic poisoning—disappear and the patient progressively improve until fairly good health and strength were established. Examples of this kind are not uncommon, I believe, as a resultant of what has appeared to be a grippal attack.

Through a contribution to the London *Lancet* in October, 1899, by A. E. Sansom, I am of the opinion that he, also, has seen cases not dissimilar. Cohnheim and Leyden have intimated that occasionally the underlying cause of uræmic symptoms is found in cardiac insufficiency. Hence, the blood stagnates in the renal vessels. Clinical observations on contracted kidneys support this view, as does the use of cardiac stimulants for the relief of their manifestations.

From the point of view of prognosis the character of the pulse is often very important. When it is relatively weak and perhaps irregular the outlook becomes serious. Sir William Broadbent has pointed out the gravity of a pulse of low tension when accompanied with symptoms indicating possible cirrhosis of the kidney. I have frequently had occasion to make a similar observation. No doubt many of these cases, however, merely enter into the category of what Sir Andrew Clark has described as "renal inadequacy" accompanied with some degree of cardiac dilatation. These are a class of cases in which, although the kidney

presented no alteration of structure, it was unable to produce a perfectly healthy urine. In these cases the urine is low in density and deficient in solid constituents, principally in urea and its congeners.[1]

I might lengthen this paper considerably. I prefer not to do so, as I very much desire a discussion as to its value and truth.

ENDOTHELIOMA OF THE SKIN DEVELOPING IN THE SCAR-TISSUE OF LUPUS VULGARIS; ANGIOSARCOMA OF THE SKIN.[2]

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of New York,
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Clinical and pathological investigations of apparently insignificant affections of the skin often yield results which have a more general application than to the special department of medicine directly concerned.

Our knowledge of malignant diseases in general has been enhanced by a study of the pre-epitheliomatous conditions of the skin, which are met with in xeroderma pigmentosum, Paget's disease of the nipple, pigmented and other moles, and in the effects of chronic irritation in stimulating epithelium to develop in the aberrant fashion met with in malignant growths of this tissue. The tumors which originate from the mesodermic structures form an even more interesting group of new growths than those which result from the proliferation of epithelium. Certain of these, as the endotheliomas, so closely resemble the epitheliomas that it is sometimes a difficult matter to differentiate them histologically; others, as the Kaposi type of multiple sarcoma, appear simultaneously on the extremities apparently independent of a parent tumor. We find again single tumors presenting all the minute structure of the angiosarcoma of Kaposi, which remain localized, do not recur after removal, and are apparently benign growths. Our knowledge of the etiological factors concerned in these new growths is, unfortunately, so meagre that no good reasons can be given for the differences met with in the clinical behavior of growths apparently alike in their structure. In certain of the infectious granulomas which are usually multiple in their manifestations we occasionally meet with one which, unable to overcome the resisting power of the tissues, or because of the slight virulence of the infectious agent, remains as a localized growth. We may invoke a similar explanation to account for the like variations in the malignancy of the connective tissue class of tumors.

[1] Albuminuria and Bright's Disease, by M. Tirard, London, 1899, p. 16.

[2] Read before the twenty-fourth annual meeting of the American Dermatological Association, Washington, D. C., May 2, 1900.

The case which forms the subject of the following brief report is interesting because of the histological structure of the growth rather than from any pronounced clinical feature of the affection.

The patient, an unmarried woman, aged forty-six years, had been afflicted for fifteen years with a chronic skin disease of the forearm. She had been under the care of several dermatologists who had made various diagnoses of the affection. Numerous applications and minor surgical procedures had been resorted to with only temporary relief.

When she came under my care I found a fairly typical patch of lupus vulgaris on the right forearm. The patch was about the size of a silver half-dollar, and was made up of scar-tissue and numerous outlying lupus nodules, the size of a pin's head and larger. A small, hard nodule, somewhat larger than a pea, was present on one side of the patch, which I looked upon in the beginning as a hypertrophied scar, the result of previous caustic applications. The lupus nodules were scraped away with the sharp curette, and chloride of zinc applied thereafter. After several attempts of this kind the lupus tissue was entirely destroyed. The nodule, to which reference has just been made, showed an increase in size, and an attempt was made to destroy it by electrolysis. Such efforts, however, only resulted in a rapid increase in its growth, and I excised it. The wound rapidly healed, but was followed by a false keloid along the line of excision, closely resembling the original growth.

As a microscopical examination of the tumor had revealed its malignant nature, I advised the patient to submit to another operation. The thickened scar was accordingly removed by an excision extending for some distance around the affected tissue. The growth removed by the second operation was found on microscopical examination free from malignancy, being composed entirely of young connective tissue.

The excised tissue was fixed in a saturated solution of mercuric chloride, embedded in paraffin and cut in series. These sections were stained with hæmatoxylin, methylene-blue and eosin, acid orcein and thionin, and by other methods. The derma throughout its entire thickness was found to be the seat of large- and small-celled masses, irregularly rounded, oval, and elongated in shape. (Fig. 1.)

The groups of cells were separated by a network of fine connective tissue fibres containing small, brightly staining, mononucleated cells; these small round cells were densely packed together about the advancing margins of the new growth. The epidermis covering the tumor was much thinned, the papillæ were obliterated, the prickle cell layer being made up of half a dozen layers of cells over which a few layers of horny cells were seen. The atrophic condition of the epidermis was evidently owing to the growth and pressure of the underlying tumor. The cell masses in the derma, most of which represented transverse sections of proliferating cells, were found in many instances arranged about central cavities containing red and white blood-cells and collections of fibrin. (Fig. 2.) In certain of these cavities a distinct lining membrane of thin, elongated cells could be made out. In others the cavities communicated directly with the surrounding cells of the new growth.

The presence of these central spaces gave to the histological picture its characteristic features, and differentiated it from an epithelioma which it so closely resembled. In none of the serial sections was there any suggestion of a connection between the growing cell masses and the epidermis or the glandular appendages.

In preparations stained with acid orcein and a nuclear dye, the absence of elastic tissue in the superficial and middle portions of the derma is well shown. The elastic fibres are, however, seen at the margins of the growing tumor and in the deeper portions of the derma.

The absence of elastic fibres may be observed in new formations in the skin, and serve to differentiate them from inflammatory and other infiltrations of this organ where such fibres can be demonstrated. Under high magnification the perivascular cells which make up the new growth are readily stained with any of the nuclear dyes. They are seen

FIG. 1. FIG. 2.

FIG. 1. Spencer one inch. No ocular. Section of the tumor under low power, showing the distribution of the new cell-growth in the derma.

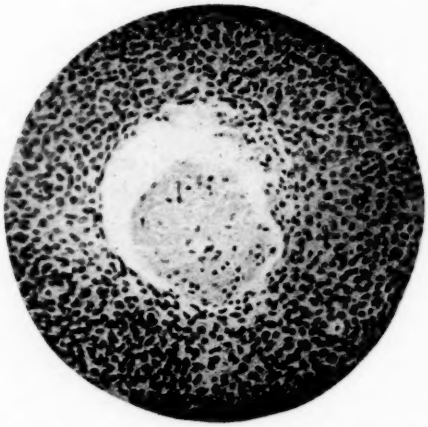
FIG. 2. Spencer half-inch. Zeiss projection, ocular 2. A transverse section of one of the cell groups under high power, showing the development of the tumor from the capillaries. The lumen of the vessel contains fibrin with red and white blood-corpuscles.

to consist of rather large, oval nuclei, densely packed together, rich in chromatin, and containing many nuclear figures. (Fig. 3.) The protoplasm surrounding the nuclei can be demonstrated by the use of a basic stain, such as eosin, orange (g) or other dyes of this character. In places, owing to the pressure of the rapidly growing cells, the nuclei assume an elongated outline which causes them to simulate spindle cells. A similar change in the shape of cells is often observed in the rodent-ulcer type of epithelioma.

From the size and appearance of the cells alone, as well as from the general conformation of many of the masses in the connective tissue spaces, it would be impossible to differentiate the growth in question from a small-celled epithelioma. The grouping of the cells about the dilated blood spaces, and their connection with the endothelial lining of the vessels, enable one readily to trace the origin of the growth to these structures, and to separate it with certainty from the epitheliomas starting in the surface epithelium, the hair follicles, or the glandular appendages. The development of a growth of the kind with lupus is, as

far as I have been able to learn, a unique observation. In spite of the malignant appearance of the cells, as shown by their numerous mitoses, we are justified, in view of the relatively benign course of these tumors in other organs as well as in the skin, in offering a better prognosis as to possible recurrence than in the epitheliomas which are met with in conjunction with lupus.

FIG. 3.



Spencer quarter-inch. Zeiss projection, ocular 2. Reduced about one-half. A similar condition to that shown in Fig. 2, but more highly magnified.

A certain amount of practical as well as scientific interest is therefore attached to a study of the case in question.

The majority of the text-books on pathological anatomy, while admitting the close resemblance of the endotheliomas to the epitheliomas, are disposed to classify them with the sarcoma group on account of their supposed origin from the connective tissue structures. Certain pathologists, however, claim that endothelium is derived from the same embryological layer as the epithelium, while others maintain that it originates from connective tissue cells.

It may be well, as has been suggested, to make a separate classification of these tumors in view of their peculiar structure and clinical course, which in some of the organs, as the skin, is rather more benign than either the carcinomas or the sarcomas. The tumors of this group which have been most carefully studied are the endotheliomas of the serous cavities and the dura mater. In the pleura they are met with as small, whitish, multiple nodules, in which the lining cells of this membrane or the lymph-vessel endothelium are primarily involved. They give rise to metastases in the bronchial glands and lungs.

In the skin there are but few recorded cases of these new growths in which their clinical as well as their pathological features have been care-

fully studied. Modern text-books on dermatology make little or no reference to their possible occurrence.

In a recent article by Spiegler,[1] which is illustrated with a number of colored and other lithographs, the author describes three cases of his own, and three other cases which he has collected from literature, in which the scalp was the seat of numerous bean- to orange-sized tumors. A remarkable similarity is shown in all the cases which are illustrated in the author's article. In addition to the great mass of tumors on the scalp small pea-sized growths were noticed in some of the cases, over the face, neck, and the upper parts of the chest and back. The clinical course of the tumors was relatively benign, as shown in their long duration, the first case reported having lasted for more than forty years.

In Ancell's case, which is reproduced from Hutchinson's *Archives of Surgery*, 1892, the patient had been afflicted with the tumors for nearly forty years; she died from metastatic involvement of the liver, peritoneum, omentum, and mesentery.

In this case three generations were afflicted in the same manner with this unusual form of new growth, and in two of Spiegler's cases father and daughter showed almost identical conditions.

The careful histological examination which Spiegler made in all of his cases revealed in one of them only a connection between the cell masses of which the tumors were made up and the capillaries. He concludes, however, in the absence of other sources of the abnormal cell growth and from the clinical and pathological similarity that they are all endotheliomas.

It may be well to refer briefly to the association of the malignant growth in my case with the long-standing lupus vulgaris. In the latter affection epitheliomas occur with sufficient frequency to indicate more than an incidental relationship. They are apt to assume fungating forms, prove rebellious to treatment, and pursue a more rapid course than when independent of such a connection.

In both syphilis and lupus the development of cancer seems to be favored by the changes which take place in the epidermis as well as those which occur in the true skin and underlying tissues. The chronic changes which these affections produce may stimulate the epidermis to proliferate while lessening the normal resisting power of the connective tissue.

The advocates of the parasitic theory of cancer look upon all association of the malignant disease with pre-existing lesions as accidental. The changes in syphilis, lupus, scar-tissue, etc., merely furnish a nidus or favorable soil on which the superadded infection more readily develops. The parasitic theory of cancer which, from the stand-point

[1] Ueber Endotheliome der Haut. Arch. für Derm. und Syph., 1899, B. l. S. 163.

of the clinician has much to be said in its favor, is not accepted by the majority of pathologists. The old hypothesis of Thiersch, which supposed that the wasting of the connective tissue in older individuals favored the down-growth of the surface epidermis by removing the barrier normally existing between the two structures, has lately been revived in a modified form under the "disturbance of balance" theory. This hypothesis, applied to the association of cancer and lupus or cancer and other chronic changes in the skin, affords an explanation which may be accepted until a better one is offered.

FIG. 4.

FIG. 5.

FIG. 4. Spencer half-inch. Zeiss projection, ocular 2. Tumor of abdomen removed from a twelve-year-old boy. Newly-formed connective tissue from the adventitia of the papillary and subpapillary vessels.

FIG. 5. Spencer quarter-inch. Zeiss projection, ocular 4. An enlarged view of a portion of Fig. 4.

The Kaposi type of sarcoma—the so-called idiopathic multiple pigmented sarcoma—is one of the best illustrations of a true angiosarcoma —*i. e.*, one in which the growth is made up on connective tissue elements, which apparently originate from the adventitia of the vessels.

The development of new bloodvessels is also a marked feature of the affection. In fact, the angiomatous element of the growths often predominates to such an extent that it is sometimes difficult to determine whether or not we have to deal with a malignant growth.

The clinical course which some of these cases pursue would seem to indicate that they are primarily angiomas, but later take on a malignant character. Histologically, the line which divides the angiomas from the angiosarcomas is not sharply drawn, as in both we have newly developed connective tissues and bloodvessels, their clinical behavior

at times being required to differentiate the one from the other. It is not difficult to understand how the unstable embryonic tissue of the angioma may at times develop a malignant growth, just as the pigmented mole reproduces its type of tissue in the pigmented carcinoma.

I have excised from the scalp of a woman, aged forty years, and a ten-year-old girl, small, brownish-red growths larger than a good-sized pea. The small tumors were almost exactly alike.

No recurrence took place as far as I have been able to determine. Under the microscope these growths were almost identical, being made up of newly developed connective tissue surrounding dilated and recently developed vessels. It would be impossible, pathologically, to distinguish the sections in these cases from those of a generalized angiosarcoma of Kaposi.

The localized variety of angiosarcoma is illustrated in the photomicrographs (Figs. 4 and 5) which were made from sections of a small warty growth from the abdomen, removed from a twelve-year-old boy.

There was considerable epithelial hypertrophy which gave the warty character to the growth. The history given by the mother of the boy was that a wart had been present for some time, but lately had been rapidly growing.

In portions of the tumor just beneath the epidermis the tissue closely resembled a benign angioma, the chief part of the growth, however, was a typical angiosarcoma in which the perivascular connective tissue cells showed numerous mitoses and were readily and brilliantly stained with the ordinary nuclear dyes. After the growth was removed the patient failed to return to the clinic, so that I am ignorant of the further course of the growth.

A COMPARATIVE STUDY OF DIGITALIS AND ITS DERIVATIVES.

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I. Digitalinum Germanicum and Digitoxin.

Introduction. The conflicting results obtained by investigators of the derivatives of digitalis, the differences of opinion which exist among clinicians as to their therapeutic value, and the importance of determining whether any of them represent the activity of digitalis, have led the writers to undertake this research. We believe that we have found certain definite causes for the diversity of results, and that we shall be

able in this paper to make some of the apparently conflicting opinions agree as to the action of these substances.

The original purpose of this paper was merely to determine the therapeutic value of digitalin, but our studies revealed so much ignorance and confusion concerning the action of the drugs belonging to the digitalis group that it seemed almost impossible to limit our investigations so narrowly. In this paper we desire to call attention to some experiments on the value of German digitalin and digitoxin compared to the tincture of digitalis, at the same time pointing out some facts concerning their effects on the circulation. In a future paper we hope to publish the results of investigation of some of the other principles of digitalis.

The digitalin and digitoxin used in this study were furnished to us by Merck & Co., and our thanks are due to them for their liberality. The tincture was the U. S. P. tincture.

It is necessary, before taking up the subject proper of this research, to consider briefly the relations of the so-called active principles of digitalis to each other. The recognized proximate principles found in digitalis are: digitalin, digitaleïn, digitonin, digitin, and digitoxin. The first four are glucosides. Digitoxin, according to Schmiedeberg,[1] is not a glucoside, but by other authors is stated to yield glucose.

All of these—except digitoxin, which belongs to the saponin group, and digitin, which is inert—have a very similar influence on the circulation.

As to the three active products mentioned, unfortunately much confusion exists. For example, the name digitalin has been applied to an amorphous product which is soluble in water, to another substance which exists in porous masses or fine scales and is insoluble in water but soluble in alcohol, and to a third body which is crystallizable and soluble in alcohol. The most important of the substances offered by various investigators as representing the activity of digitalis are: digitalinum Germanicum, digitalin crystalisée of Nativelle, digitalin of Homolle and Quevenne, digitalin of Kiliani, digitaleïn and digitoxin of Schmiedeberg.

It seems probable from the literature that the digitalin of Homolle and Quevenne is an impure form of digitalin crystalisée, which seems to be identical with digitoxin, and that digitalinum verum of Kiliani is the digitaleïn of Schmiedeberg. According to Schmiedeberg, digitalinum Germanicum is a mixture consisting largely of digitaleïn. It has also been stated that digitalinum Germanicum contains digitoxin. This statement seems to us extremely improbable, as digitoxin is almost entirely insoluble in water, while German digitalin dissolves readily in water. If digitoxin is present in digitalin as such we do not see how it is possible for the mixture to dissolve completely in water unless there be present some unknown solvent in digitalin.

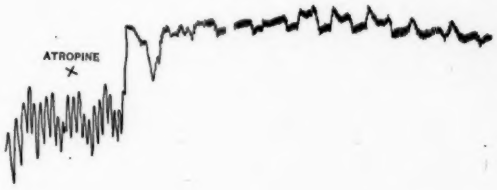
A plausible explanation of the discrepancies in the results of chemical investigations is that these substances, known to undergo chemical changes with comparative ease, may be altered by the manipulations required to separate them.

Viewed from the stand-point of its physiological action, we believe the digitalinum Germanicum furnished by Merck to be a uniform product and stable in its composition. In regard to its stability, we may say here that we obtained identical results with some which had been in the laboratory more than two years and that sent to us direct from the manufacturer in sealed containers.

The most important practical question is whether any of these substances represent the therapeutic activity of digitalis. It seems useless to continue with the apparently endless discussion as to their chemical relations.

General Action on the Circulation. Our studies of the blood-pressure were mostly made on dogs, the drugs being given intravenously. The results obtained were so uniform that it will only be necessary to give the details of a few experiments which may be considered as representing very fairly the general results of our work. In addition to this a number of tracings and tables have been appended, and from these the reader may draw his own conclusions.

Fig. 1.



Animal has received 0.01 gm. digitoxin. + = injection of 0.02 gm. atropine sulph. Showing the abolition of the effect of digitoxin on the pulse rate, and the accompanying sudden rise of pressure.

Tincture of Digitalis administered to a dog weighing 16.8 k., in doses of 1 c.c. to 2 c.c. (see Table I.), produced the following results: After 2 c.c. had been given the blood-pressure rose from 136 mm. to 154 mm., and the pulse rate decreased from 210 to 114. After 2 c.c. more the rate was 65. The pulse waves were enormous in size (16 mm.), and the blood-pressure rose to 190 mm. Suddenly, after this condition had per-

sisted for one minute, the pulse rate increased to 228 and the pressure fell to 148 mm. The pulse waves were very small. This condition of rapid pulse continued after further dosage, and the pressure remained about the same. The only change observed was that the pulse became somewhat irregular. After the final dose the heart suddenly ceased beating, and upon rapidly opening the thorax was found in diastole. The right ventricle responded to stimulus, but the left did not.

That the change in the pulse rate was due to vagal influence is shown by Experiment II. (see Fig. 1), in which 0.02 gramme of atropine sulphate caused an immediate increase in the rate of the heart beats from 42 to 198 per minute, with an accompanying rise of pressure. In this experiment as the rate of the pulse increased the size of the individual waves diminished, remaining, however, always larger than the normal. A further injection of 2 c.c. of digitalis caused a fall of pressure to 124 mm., while the rate remained 198. After a final dose of 3 c.c. the heart almost at once ceased beating, and immediately afterward was found in diastole and non-irritable.

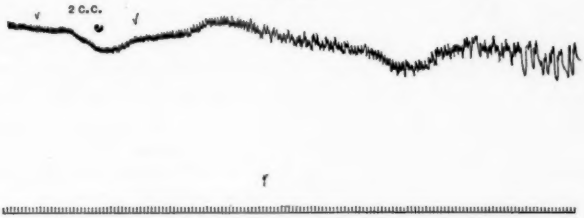
Digitalin administered to a dog weighing 8.4 kilos in doses of from 0.02 gramme to 0.4 gramme (see Table III.) caused after a dose of 0.04 grammes a rise of blood-pressure from 114 mm. to 120 mm., and a reduction of rate from 108 to 87. After another dose of 0.02 gramme the rate was 63 and the pressure 140 mm. The pulse waves were large and occasionally dicrotic. After 0.04 gramme more had been given the pressure was 144 mm. and the rate 84. Suddenly, without any preliminary alteration in rate or pressure, the rate rose to 126 and the pressure to 159 mm., the pulse waves becoming much smaller and somewhat irregular. Very shortly after 0.04 more gramme had been given the heart stopped and was found in diastole and did not respond to stimulation. (See Table XI.).

Digitoxin (see Table IX.) given to a dog weighing 9.2 kilos produced, after administering 0.12, a rise of pressure from 146 mm. to 166 mm., and a decrease in rate from 162 to 156. The administration of 0.12 gramme more reduced blood-pressure to 126 mm. and the rate to 90. Another dose of 0.04 reduced the rate to 84, while the pressure rose to 172 mm. Very suddenly and nearly a minute after 0.08 gramme more had been given the pressure rose to 192 and the rate to 186. Forty seconds later the heart suddenly ceased beating, and was found in diastole and responded very feebly to stimulus.

Quite commonly immediately after an injection of digitoxin had been given a marked fall of pressure was observed (see Fig. 2*a*), but as the drug was given in alcoholic solution and the condition lasted only for a few seconds, we attribute the effect to the presence of the alcohol. It is possible that the irritant action of digitoxin may be partly responsible for this effect.

It will be readily seen from the foregoing statements that there is little if any difference in the general action of these three drugs on the circulation. In each there is seen a rise in the pressure preceding a slowing of the pulse. As a rule the pressure remained high during the period of slow heart-action, although in one experiment with digitalis it fell 6 mm. (see Table II.). After larger doses the rate of the heart became very slow, the pulse waves very large, and during this period

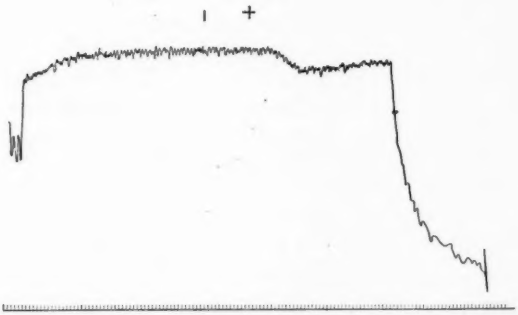
FIG. 2a.



Digitoxin 1 — + = injection of 0.004 gm. digitoxin. Time 5′.

Showing the primary fall of pressure following intravenous injection, due either to the alcohol or perhaps to the irritant action of the drug itself.

FIG. 2b.



Five minutes later than (*a*). Has received previous to curve 0.024 gm. digitoxin
1 — + = injection of 0.004 gm. digitoxin.

Showing sudden paralysis of the pneumogastrics with rise of pressure, and the sudden heart failure following the fatal injection.

sometimes quite a marked fall of pressure occurred (see Table II.); but, on the other hand, it might be elevated. Pulse waves were sometimes dicrotic (see Fig. 3). With surprising suddenness there followed an enormous increase in the rate of the heart, often with a marked and precipitous rise of pressure (see Table X. and Fig. 2*b*.). Sometimes, however, for some reason this increase in the rate of the heart did not elevate the pressure, an indication that perhaps the muscle was

weakened coincidently with the pneumogastric. The pulse remained regular for a period, usually later becoming markedly irregular. If more of the drug was administered the heart almost at once ceased to beat, and was found in diastole and practically non-irritable.

FIG. 3.

Time 1 — + = injection of 0.04 gm. digitalin.
Showing the rise of pressure despite slowing of the pulse.

Let us now consider the causes of the effects obtained. The slowing of the heart is undoubtedly due to stimulation of the cardio-inhibitory mechanism, limited chiefly to the peripheral part of this apparatus, as it is not prevented by previous section of the vagi (see Table VIII.), and is prevented or abolished by atropine (see Tables II., VI., and Fig. 4.)

FIG. 4.

Has received 0.025 gm. atropine sulphate. 1 — + = injections of digitalin.
Showing the powerlessness of digitalin to slow the atropinized heart, proof that the slowing is an action on the inhibitory nerves.

In this statement we are supported by Brunton,[2] H. C. Wood,[3] Butler[4] and Cawarjee[7] and Cresburg.[5] Francois Franck states that the slowing of the rate is not due to action on the vagus, but we are unable to see in what manner he has arrived at his conclusions. We feel that our own evidence on this point is quite conclusive. L. Traube[6] states that, after section of the vagi, soluble digitalin in warm-blooded animals was with rare exceptions incapable of reducing the pulse rate. We

found, to the contrary, that slowing occurred in all our experiments under these conditions. That the slowing is partly due to stimulation of the vagus centre is shown in Table VII., by the increased rate produced by section of the pneumogastrics after slowing had been brought about by digitalin. This view is upheld by Brunton. Boehm[13] states that atropine is powerless to affect the digitalis pulse-rate in frogs; we have not experimented on these animals, but have proven that the statement is not true of the dog.

The rise in blood-pressure is partly due to increased cardiac power, but seems to us more to a constriction of the blood paths. Reference in support of this statement may here be made to H. C. Wood, Biddle, Butler, Hale White,[9] Ringer and Sainsbury,[10] Brunton, Donaldson and Stevens,[11] and others. We cannot agree with the opinion of Ackerman[12] that the rise of pressure is entirely of cardiac origin. Although there is no doubt that the individual beat is much stronger than normal, nevertheless the pulse is so much slowed that we doubt if the heart does a greater amount of work, which conclusion agrees with the results of Donaldson and Stevens and of Klug.[8]

In accord with this we sometimes found a distinct fall in the pressure, doubtless to be explained by the slowing of the pulse, the drug failing for some reason to produce consentaneous increase in the muscle power. At no time did we observe a fall which could be attributed with certainty to depression of the vasomotor mechanism. The sudden rise of pressure with great increase in the pulse rate in the later stages of the poisoning is undoubtedly due to paralysis of the cardio-inhibitory apparatus, as stimulation of the vagus at this time does not produce the usual slowing of pulse-rate (see Table XI.).

As will be shown hereafter, the final sudden cessation of the heart's action is due to a direct paralyzant action on the heart muscle and not to excessive vagus stimulation. It is not prevented by previous paralysis of the inhibitory mechanism by atropine, and, as has been stated above, paralysis of the vagi was uniformly observed in the later stages of the poisoning.

HEART. It is the common custom to study the cardiac effects of drugs on the isolated heart of the frog, and digitalis with its various principles forms no exception to this rule. But the value of such investigations we think is much overestimated, and that it is a mistake to draw too positive conclusions concerning their action on the human economy from such evidence. The contradiction between our results and the common teaching concerning this group of drugs first led us to doubt the reliability of experiments on the batrachian heart, and we think a careful review of the work of various investigators in this field will convince anyone, as it has us, that a method which leads to results so diverse must contain some serious error. There are many theoretical

objections which can be urged against this mode of experimentation, and it is not at all necessary to assume any inherent difference between the muscle-fibre of the heart of warm and cold-blooded animals, although it seems not at all improbable that such difference does exist.

As has been pointed out by Masi,[14] in his studies with digitalin, the temperature of the organ plays an important rôle in its susceptibility and manner of response to poisons. Masi showed that the frog's heart, which ordinarily is arrested in systole by digitalin, would when warmed to 32° C. stop in diastole, and that, conversely, the mouse's heart if cooled remained in systolic spasm after poisoning by the drug. Furthermore, the other conditions under which the isolated frog heart is laboring are so widely different from those of the mammalian heart *in situ* that one might well be surprised that the results should be at all similar. Donaldson and Stevens called attention fifteen years ago to the effect which the high pressure on the venous side of the artificial circulation has on the work of the heart, and by using methods more nearly approaching the normal conditions achieved results quite different from those of previous observers. It is not necessary to go into all the circumstances in detail that can affect the action of drugs on the heart, for no more convincing argument of the faultiness of such methods can be put forward than the widely varying conclusions that different observers have reached.

The one fact on which all investigators seemed agreed is that ordinarily the isolated frog's heart is arrested in systole by the substances under consideration. According to Dybkowsky and Pelican (quoted by Boehm), this is true only of the ventricle, the auricles stopping in diastole. Boehm[15] found that moderate doses of digitalin sometimes caused the frog's heart, when not separated from the central nervous system, to cease beating in diastole from excessive inhibitory stimulation. The systolic spasm has been found by Klug to follow digitoxin also.

Our few experiments on the frog's heart were made with digitalin and digitoxin, to see if any difference in their action from digitalis could be here detected rather than to determine their pharmacological properties. We used the isolated ventricle of the frog's heart with Kronecker's apparatus. For a nutrient fluid a mixture of one part of blood and nine parts of salt solution (0.7 per cent.) was employed.

A digitalin of one-quarter per mille was in all cases sufficient to send the heart into tetanic contraction; indeed, one-eighth per mille was in most cases strong enough. In a heart which was beating spontaneously one-quarter per mille solution produced a condition in which the ventricle relaxed slowly, but as the next contraction began immediately after the relaxation of the previous one there was no distinct slowing of the cardiac rate. At no time could any marked change in the rate be demonstrated, nor was there any increase in the force apparent, the pulse

wave remaining the same height until imperfect diastole lessened it. In the heart stimulated by electricity a very similar state of affairs was observed, with, however, one additional feature of interest. There occurred a stage where, if the impulses were sent at short intervals (60 per minute), the heart would pass into the systolic spasm, but would slowly relax on interruption of the current; if the excitations were separated by a wide enough interval of time the heart would contract and relax perfectly, albeit very slowly. No qualitative difference in the action of digitoxin was detected.

Mammalian Heart. Attention has already been called to the fact that the heart of the warm-blooded animal does not react to these poisons in the same manner as does that of the cold-blooded, and we may now call attention to some of the points of difference. In review of the effects of digitalis on the general circulation we have already mentioned the fact that on opening the chest we invariably have found the heart in diastole. This condition has already been too often described to need any further discussion were it not that Franck denies the truth of it. This investigator affirms that the belief that the heart stops in diastole is due to imperfect methods of observation, and claims to have shown with other methods that it really ceases beating in a state of contraction. He explains the failure of previous experiments to reach the same conclusion by the assertion that this systolic spasm is of very short duration, and that before the chest can be opened the heart has relaxed with fibrillation. After careful study by the method to be described immediately we are unable to agree with Franck, and feel ourselves justified in the statement that in the majority of cases the heart is arrested in diastole. In Experiment III. the termination was such as to allow of a dispute concerning the meaning of the phrase "stop in systole." It is hardly proper in our opinion to speak of a heart having ceased to beat when it remains in the same state of contraction for only a fraction of a second; of course, its last contraction must have brought it into the position of systole, and when systole was done it ceased contracting, but by the same argument it might be shown that the heart always "stops in systole."

Our opinion concerning the death of the heart is based on our cardiac and blood-pressure curves, and on careful studies made to ascertain especially this point by direct observation in the following manner: The jugular vein having been exposed and a canula placed in it, tracheotomy was done and artificial respiration established. The chest was then opened in the median line with especial care to prevent hemorrhage as much as possible; the chest walls were then separated and held apart by chain hooks. The movements of the heart were studied by the eye and finger, and note made both of what we felt and what we saw. As we both saw exactly the same things, and as the phenomena

were of a nature so unmistakable, we think equal or even greater confidence may be placed in it than any graphic method.

In a dog weighing 7 kilos, 5 c.c. of the tincture of digitalis caused the cardiac beats to become slower and more forcible. An additional 5 c.c. brought about only an increase in these effects. After 3 c.c. more the diastolic pauses were very long, and then with most striking suddenness the heart began to beat with extreme rapidity. At first the contractions were regular and moderately full, but later, systolic impulse continually growing relatively stronger than the diastolic, the movements become more and more rapid until finally by imperceptible gradations they were no more than inco-ordinate fibrillary contractions and the organ relaxed, still showing after relaxation in a typical form the "flimmerbewegung" described by Kronecker.[15]

It is very easy to conceive that if one were trusting to a graphic method the excessively rapid and minute contractions at the instant when the heart began to fibrillate might easily be overlooked and the heart supposed to be remaining still in systole at this time.

Parallel experiments were done with digitalin and digitoxin, but did not reveal any distinct difference between them and digitalis, and the results are given in tabular form:

EXPERIMENT II.—Digitalin. Dog, weight 6 kilos.

8.51	Thorax opened.
8.52	Heart irregular and weak, 76 per minute.
8.54	Injection 0.10 gm. digitalin.
8.55	Heart stronger and more regular, 72 per minute.
8.56	Heart 212 per minute, systole hard, diastole imperfect.
8.56½	Heart beating excessively rapid.
8.57	Heart fibrillating, stops in diastole, non-irritable.

EXPERIMENT III.—Digitoxin. Dog, weight4. 7 kilos.

9.19	Thorax opened.
9.20	Heart fairly strong, 168 per minute.
9.21	Injection of 0.01 digitoxin.
9.21½	Occasional diastolic pauses.
9.22	Heart shows a tendency to beat in groups of two, 72 beats per minute.
9.23	Heart 52 per minute.
9.25	Left auricle 176 per minute, left ventricle 72 per minute.
9.25½	Auricle and ventricle in accord 200 per minute; systole is hard and diastole imperfect.
9.27	Heart very rapid, counted 264 per minute.
9.27½	Left ventricle stops and immediately relaxes.
9.27.50″	Right ventricle stops and immediately relaxes.
	Right ventricle responds to stimulus, left does not; no fibrillating in either.

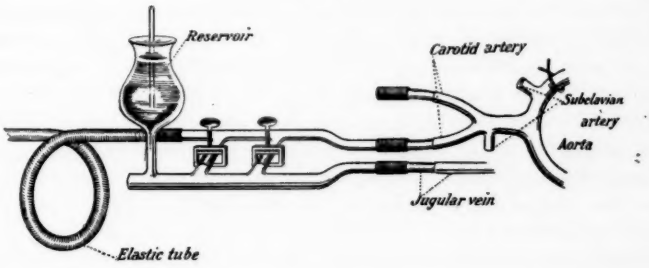
Overwhelmingly large doses of these drugs seem to paralyze the heart muscle directly without inhibitory paralysis, and very promptly, as is shown by the following experiment:

EXPERIMENT IV.—Digitalin. Dog, weight 3.8 kilos.

12.05	Thorax opened.
12.06	Heart 186 per minute.
12.06½	Inject 0.10 gm. digitalin.
12.07	Heart 42 per minute.
12.09	Inject 0.10 gm. digitalin.
12 09½	Heart stops in diastole ; no fibrillation.

More elaborate studies of the effect of digitalis on the mammalian heart were made with the method described by J. Bock.[16] The method did not yield in our hands quite so satisfactory results as those that its originator seems to have obtained, but has points which make it a method of some value. As practised by us, Bock's method is as follows : The trachea is exposed in the ordinary manner and a respiratory canula inserted. The pectoralis major and sternomastoid muscles are then separated from their sternal attachments. A stout ligature is placed around the sternum on a level with the first rib, and the tip of the

FIG. 5.



bone above the ligature is cut away with bone forceps, exposing the subclavian arteries, which are ligated. Tension is made on the ligature attached to the sternum, and with the left subclavian as a guide careful dissection is made down to the aorta, around which a ligature is placed, but not tied. A large canula is then inserted into one jugular vein low down. Artificial respiration is now begun, and one carotid connected with a manometer. The other carotid is connected with a series of glass tubes (see Fig. 5) representing the peripheral vessels. These tubes are filled with leech extract and supplied from a reservoir with a dilute solution of the same. Immediately before ligating the aorta, which is the final step in the operation, an intravenous injection of leech extract, made so that one leech head is given for each kilo body-weight, is given in order to prevent coagulation of the blood. As a test of the thoroughness of the ligation of the aorta we used the femoral pulses, which, of course, are absent if the vessel is entirely occluded.

Bock states that under such conditions cardiostimulants cause a rise of pressure in the manometer, and mentions the digitalis-like poison, helleboreine, as causing such a rise. We ourselves never obtained any such elevation of the pressure by digitalis, but are inclined to attribute our failure to faulty technique rather than to lack of power of the drugs.

The first effect of digitalin and digitalis was to cause a slowing of the pulse. In Experiment XI. with digitalis, as section of the vagi caused an increase in the pulse rate, it is evident that the centres in the medulla were not absolutely dead, probably one of the subclavians was insecurely tied. Simultaneously with the decreased rate an increased force of the pulse is to be noted. This increase in the pulse-wave varied always parallel to the slowing, and might be well due to the inhibitory stimulation. In Experiment XI. the same course of events as described in the blood-pressure curves is seen, namely, the sudden increase in the rate of the heart due to inhibitory paralysis (as is shown by the powerlessness of the electric current to inhibit the cardiac action).

In Experiment XII. we have, however, a very different termination. The heart, instead of becoming very rapid, becomes very slow and full. This condition was entirely independent of any inhibitory influence because it was not affected by atropine. The exact signification of this experiment we are unable to determine; the most plausible explanation we have to offer is that under the drug the muscle was increased in its extensibility (see Donaldson and Stevens), undergoing a sort of dilatation with little loss of power. At the same time the irritability of the muscle was depressed so that an ordinary degree of intracardiac pressure was unavailing to excite, and the heart refused to respond until overdistended with blood, while the capability for contraction was unaffected. Experiment III., in which we found the auricles beating two or three times as fast as the ventricles, may have some interest in this connection, although, of course, in that case the heart was under the influence of pneumogastric stimulation.

Dosage. From the foregoing account of our experiments it is seen that both digitalin and digitoxin are circulatory stimulants of considerable power, resembling closely, if not identical with, digitalis tincture in their pharmacological activities. Nevertheless neither of them has achieved such clinical results as to gain the full confidence of the profession, the general verdict being that digitalin is "uncertain" in its action. It is hard to see why an active principle representing, as this one seems to, the full therapeutic virtue of a drug, should be less uniform in its results than the cruder preparation. And it is to our minds equally as improbable that a substance should affect so powerfully and certainly the circulatory system of a dog and not that of man. In this connection it may be remembered that some years ago the tincture of digitalis was dubbed "uncertain," but since we have learned to

give it in equivalent dose it has proven itself equal to the infusion in efficiency. We think the same mistake concerning digitalin is hindering the profession from the use of a valuable remedy. Ordinarily the dose is stated to be 1 to 2 milligrammes ($\frac{1}{60}$ to $\frac{1}{30}$ of a grain), and the clinician blames the drug for failing to act. Several years ago Dr. Beates[22] quite startled some of the more conservative practitioners of medicine by advising them to give digitalin in half-grain (0.12 gramme) doses, and telling of excellent results achieved in this way. Dr. Beates' doses agree so closely with those that we have arrived at by reasoning from our experiments that it seems surprising no one else has before this confirmed his statements.

From the appended tables it will be seen that the smallest amount of the drug which caused any distinct symptoms of poisoning was 3.5 milligrammes per kilo, while in no case did less than 7.5 milligrammes prove fatal. If we estimate the weight of a man at 70 kilos (157 pounds), it would require to cause any toxic manifestations 0.245 gramme.* Moreover, it is to be remembered that these amounts were injected intravenously, and consequently reached the vital centres in a much greater concentration than if the remedy had been taken by the mouth. The doses given in our tables agree closely with those of Boehm and are somewhat smaller than those of Bardet.

DIGITALIN.

Experiment.	Weight of dog.	Toxic† amount.	Fatal amount.	Toxic amount per kilo.	Fatal amount per kilo.	Remarks.
	5.5 kilos.	0.04 gm.	0.080 gm.	0.0073 gm.	0.0146 gm.	
Exper. III.	8.4 "	0.04 "	0 18 "	0.0048 "	0.0214 "	
" VIII.	8.0 "	0.04 "	0.06 "	0.0050 "	0.0075 "	Vagi divided.
	12.3 "	.....	0.16 "	.....	0.0130 "	Atropinized.
" VI.	17.0 "	0.06 "	0.22 "	0.0035 "	0.0139 "	Atropinized.
" II. (p. 174)	6.0 "	.....	0.10 "	.....	0.0167 "	

DIGITOXIN.

Table X.	11.5 kilos.	0.016 gm.	0.028 gm.	0.0014 gm.	0.0024 gm.	
" IX.	9.2 "	0.012 "	0.036 "	0.0013 "	0.0039 "	
	5.0 "	0.010 "	0 020 "	0 0020 "	0.0040 "	Atropinized.
Exper. II. (p. 174)	4.7 "	.....	0.010 "	.....	0.0021 "	

There are, however, several objections which may be argued against conclusions arrived at in such a manner. In the first place, of course, we do not wish to poison our patient. To this we would say that the amount given (0.25 gramme) represents the physiological limit for the

* Approximately, 3½ grains.

† Fall in the pulse-rate of ten beats per minute was regarded as a toxic manifestation.

dog. Two objections which are more valid are the well-known cumulative action of digitalis and the difference in susceptibility of the human and canine organisms. The most rational procedure to determine the therapeutic dose under these circumstances seems to us to be to compare its relative power to such a well-known preparation as the tincture of digitalis. The lethal dose for a dog of this tincture may be put at about 1 c.c. per kilo (see Tables I. and II.), and the toxic dose at about 0.3 c.c. per kilo body-weight. The average fatal dose of digitalin for the dog was in our experiments 0.0145 per kilo of body-weight, and the toxic dose 0.0051. These figures will be seen to agree very closely with those of the tincture in the relation between poisons and fatal doses. We may safely state, then, that 0.015 gramme (¼ grain) of digitalin about equals 1 c.c. (16 minims) of tincture of digitalis representing 0.15 gramme of the leaves. We hope in a future paper to report clinical confirmation of these doses.

As for digitoxin, Koppe[17] gives the fatal dose as 1.5 milligramme per kilo, and Franck[21] as 2.3 milligrammes per kilo. In our own experiments the average fatal dose was 3.1 milligrammes per kilo. By averaging all these results and reasoning as above we would obtain 0.0023 as the therapeutic dose for a man. Koppe, however, poisoned himself quite severely with a single dose of 0.002 gramme, although 0.001 gramme had no effect on him three days previously. Wenzel,[18] von Starck,[19] and Masius[20] all report good effects from digitoxin in doses of ¼ to ¾ milligrammes several times a day. The irritant properties, however, of this drug render it less fit for human medication on account of the liability to upset the stomach if given per os, or to cause abscesses if given hypodermatically. Another objection to its use is its insolubility, which renders it irregularly absorbed and slowly eliminated, and hence very liable to accumulate in the system or to act with varying degree of power.

Conclusions. 1. Digitalin and digitoxin each represent the full circulatory powers of digitalis.

2. Digitalis, digitalin, and digitoxin stimulate the cardio-inhibitory mechanism both centrally and peripherally. In larger doses they paralyze the intrinsic cardio-inhibitory apparatus.

3. They all cause a rise of blood-pressure by stimulating the heart and constricting the bloodvessels.

4. Very large doses paralyze the heart muscle of the mammal, the organ stopping in diastole.

5. Digitalin of Merck is a stable compound, one gramme of it being equivalent to about 70 c.c. of tincture of digitalis.

6. Digitoxin is not to be recommended for human medication on account of its irritant action, which makes it liable to upset the stomach when given by the mouth or to cause abscesses when given hypoder-

matically, and on account of its insolubility, which renders it slowly absorbed and irregularly eliminated, having a marked tendency to cumulative action.

TABLE I.—Tincture Digitalis. Dog, weight 16.8 kilos.

Time.	Press.	Pulse.	
Beginning	136	210	
0′ 25″ } 0 30 }	.....	.....	Injected 1 c.c. tincture digitalis.
1 0	144	216	
1 25 } 1 30 }	.....	.....	Injected 1 c.c. tincture digitalis.
2 10	156	210	Pulse about normal.
3 30	174	246	Pulse about normal.
4 10	154	114	Pulse large, regular.
5 40	146	234	Pulse small, regular.
6 0 } 6 5 }	.....	.....	Injected 1 c.c. tincture digitalis.
6 40	156	102	Pulse waves very large, regular.
7 40 } 7 45 }	.....	.....	Injected 1 c.c. tincture digitalis.
8 20	190	65	Pulse waves 16 m.m. and dicrotic.
9 20	148	228	Pulse waves small, regular.
9 30 } 9 35 }	.....	.....	Injected 1 c.c. tincture digitalis.
10 5 } 10 10 }	.....	.....	Injected 1 c.c. tincture digitalis.
10 50 } 11 0 }	.....	.....	Injected 2 c.c. tincture digitalis.
11 30 } 11 35 }	.....	.....	Injected 2 c.c. tincture digitalis.
12 10	150	246	Pulse waves small and irregular.
13 30 } 13 40 }	.....	.....	Injected 2 c.c. tincture digitalis.
14 0 } 14 10 }	.....	.....	Injected 2 c.c. tincture digitalis.
14 40	148	222	Pulse waves small and regular.
15 10 } 15 20 }	.....	.....	Injected 2 c.c. tincture digitalis.
15 30	.....	.....	Heart stopped beating; thorax opened quickly, and heart found in diastole. Right ventricle responded to stimulus, left ventricle did not respond. After massaging heart for a few minutes both ventricles responded to stimulus, but only feebly.

Total dose, 16 c.c. tincture.

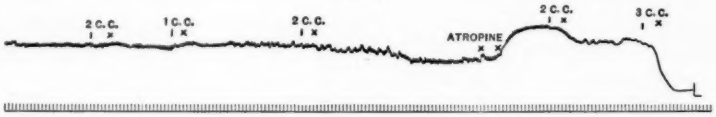
TABLE II.—Tincture Digitalis. Dog, 9.8 kilos

Time.	Press.	Pulse.	
Beginning	122	198	
1′ 20″ } 1 30 }	.....	.....	Injected 2 c.c. tincture digitalis.
2 0	116	114	
2 10 } 2 15 }	.....	.....	Injected 1 c.c. tincture digitalis.
3 0	122	108	Fig. 6.
3 50 } 4 0 }	.....	.....	Injected 2 c.c. tincture digitalis.
5 0	84	42	Pulse waves large and regular.
6 0 } 6 10 }	.....	.....	Injected 0.02 gm. atropine sulphate.
6 30	160	198	Pulse waves larger than normal, and regular.

Time.	Press.	Pulse.	
6′ 40″ }	.....	.....	Injected 2 c.c. tincture digitalis.
6 50 }			
7 10	124	198	Pulse waves small and regular.
7 40 }	.....	.....	Injected 3 c.c. tincture digitalis
7 50 }			
7 55	.....	.....	Heart stopped. Heart in diastole—Flimmer. Does not respond to stasis.

Total dose, 10 c.c.

FIG. 6.



1—+ = injections of tincture digitalis.

TABLE III.—Digitalin. Dog, weight 8.4 kilos.

Time.	Press.	Pulse.	
Beginning	114	108	
0′ 30″–0′ 50″	.....	.....	Injection 0.04 gm. digitalin.
1 0	120	87	
1 20—1 30	.....	....	Injection 0.02 gm. digitalin.
1 35	140	63	Pulse waves large, occasionally dicrotic.
2 15–30	.....	.....	Injection 0.02 gm. digitalin.
3 0–15	.....	.....	Injection 0.02 gm. digitalin.
3 30	144	84	
4 15	159	126	Heart somewhat irregular.
4 20–30	.....	.....	Injection 0.02 gm. digitalin.
5 0	.....	.....	Injection 0.02 gm. digitalin.
5 20	150	168	Pulse waves small.
9 0	156	190	
9 15–30	.....	.....	Injection 0 02 gm. digitalin.
9 30	.....	.....	Heart stopped. Chest opened; heart found in diastole, and not irritable.

Total digitalin, 0.18 gm.

TABLE VI.—Digitalin and Atropine. Dog, weight 17 kilos.

Time.	Press.	Pulse.	
Beginning	142	96	
0′ 5″	.....	.....	Inject 0.02 gm. atropine sulphate.
1 10	.....	.....	Inject 0.05 gm. atropine.
1 40	136	150	
1 45	.....	.....	Inject 0.04 gm. digitalin.
2 05	.....	.....	Inject 0.02 gm. digitalin.
2 55	168	162	
4 0	.....	.....	Inject 0.04 gm. digitalin.
4 20	96	162	
4 50	.....	.....	Inject 0.04 gm. digitalin.
5 15	.....	.....	Inject 0.04 gm. digitalin.
6 20	190	192	
6 25	.....	.....	Inject 0.04 gm. digitalin.
6 45	159	.....	
7 10	224	204	Inject 0.04 gm. digitalin.
7 15	.....	.....	
7 40	.....	.....	Heart stops. Chest opened; heart in diastole; does not respond to stimulus. Respiratory movements persist after cardiac arrest.

Total digitalin, 0.22 gm.

TABLE VII.—Digitalin. Dog, weight 9.5 kilos.

Time.	Press.	Pulse.	
Beginning	80	84	
0′ 10″–20	.....	.....	Inject 0.02 gm. digitalin.
1 20	104	69	
4 30-40	.....	.....	Inject 0.04 gm. digitalin.
5 0	122	72	
5 25	.....	.....	Both vagi divided.
5 30	153	126	Experiment ended.

TABLE VIII.—Digitalin. Dog, weight 8 kilos

Time.	Press.	Pulse.	
Beginning	167	174	Both vagi have been divided.
0′ 10″–20	.....	.....	Injection 0.04 gm. digitalin.
1 0	200	90	
2 40	140	186	Pulse waves small.
7 0	210	240	
8 0–10	.....	.....	Injection 0.02 digitalin.
9 20	.....	.....	Heart stopped. Chest opened; heart found in diastole, right side irritable, left not. Respiratory movements continued after heart had ceased.

TABLE IX.—Digitoxin. Alcoholic Solution. Dog, weight 9.2 kilos.

Time.	Press.	Pulse.	
Beginning		146	162	
0′ 45″–0′	58″	.....	.....	
1 10		156	180	Injection 0.004 gm. digitoxin
1 30 — 1	40	.....	.....	
2 20		160	150	Injection 8 mgm. digitoxin.
2 30 — 2	35	.....	.....	
3 10		150	90	Injection 8 mgm. digitoxin.
3 20 — 3	25	.....	.....	
4 0		126	90	Injection 4 mgm. digitoxin.
4 10 — 4	15	.....	.....	
4 50 — 5	0	.....	.....	
5 30		172	84	Injection 4 mgm. digitoxin.
6 10		192	186	Injection 8 mgm. digitoxin.
6 50		.....	.....	Pressure fell to 0 rapidly; heart stopped.
7 0		.....	.....	Vagi cut; no effect. Heart in diastole; responds feebly to stimulus. Massage causes weak beats for a few seconds.

Total dose, 0.036 mg.

TABLE X.—Digitoxin. Dog, weight, 11.5 kilos. Chloretone anæsthesia.

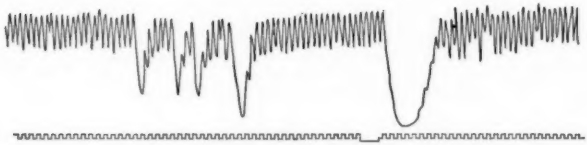
Time.	Press.	Pulse.	
Beginning	130	192	
0′ 5″	.....	.....	Inject 0.002 gm. digitoxin alcoholic solution.
0 45	142	192	
1 0	.....	.....	Inject 0.002 gm. digitoxin solution.
1 30	156	190	
2 10	.....	.....	Inject 0.004 gm. digitoxin.
2 50	172	190	
3 0	.....	.....	Inject 0.004 gm. digitoxin.
4 10	.....	.....	Inject 0.004 gm. digitoxin.
4 40	174	180	Pulse waves slightly larger.
5 20–40	.....	.....	Inject 0.008 gm. digitoxin.
6 0	176	162	
7 30	136	120	Deep inspirations
8 20	120	60	
8 40	220	252	
9 10	.....	.....	Inject 0.004 gm. digitoxin.
9 30	.....	.....	Heart stops. Chest opened; heart found in diastole responding feebly to stimulus.

Total amount digitoxin, 0.028 gm. Per kilo. 0.0035.

TABLE XI.—Bock's Method. Tincture of Digitalis. Dog.

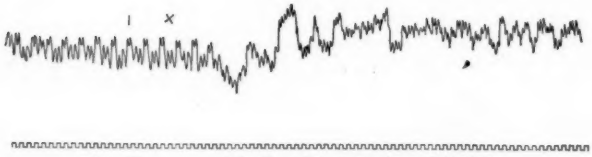
Time.	Rate of pulse.	Height of pulse.	
Beginning	126	18	
0′ 10″–30	.....	...	Injection 1 c.c. tincture digitalis.
1 30	114	18–24	
8 0	126	17	
8 5–8 15	.....	...	Inject 1 c.c. tincture digitalis.
9 15	114	17	
13 0	.....	...	Inject 2 c.c. tincture digitalis.
14 0	99	23	
14 30–40	.....	...	Inject 2 c.c. tincture digitalis.
15 20	84	31	Occasional diastolic pauses (Fig. 7).
16 30 }	.....	...	Two vagi successively cut.
17 30 }			
17 35	111	20	
18 30	.....	...	Inject 1 c.c. digitalis (Fig. 8).
19 30	156	8–14	
19 35	.....	...	Inject 1 c.c. tincture digitalis.
20 0	168	7	Systole hard, diastole never complete.
28 0	162	10	Electrical stimulation of vagus without effect.

FIG. 7.



Time 15′–16″. Has received 6 c.c. tincture of digitalis.

FIG. 8.



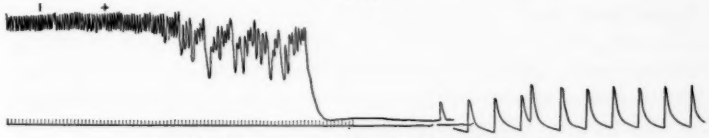
Time 18′. I — + — injection of 1 c.c. tincture of digitalis.

TABLE XII.—Bock's Method. Digitalin Germanicum. Dog, weight 7.1 kilos.

Time.	Rate of pulse.	Height of pulse.	
Beginning	123	14	
0′ 10″ }	.....	...	Injection 0.004 gm. digitalin solution.
1 10 }			
2 10	96	20–32	Periodically occurring vagus pulses.
3 30	.....	...	It was here found that the aorta was not
7 0	114	25	[securely ligated.
7 30 }	.....	...	Inject 0.002 gm. digitalin.
8 30 }			
9 0	114	26	
12 0 }	.....	...	Inject 0.004 gm. digitalin.
12 45 }			
13 15	126	19	
22 0	108	17	

Time.	Rate of pulse.	Height of pulse.	
22′ 10″ }	.....	...	Inject 0.004 gm. digitalin.
22 15 }			
23 0 }	.....	...	Inject 4 mg. digitalin.
23 20 }			
24 0–15	.....	...	Inject 4 mg. digitalin.
25 0 }	.....	...	Inject 4 mg. digitalin.
25 15 }			
25 35	105	22	
25 40–55	.....	...	Inject 4 mg. digitalin.
26 25	72	24–32	Long diastole pauses (Fig. 9).
26 40	.....	...	Heart stops for twenty seconds.
27 20	10	52	(Fig. 9.)
28 0	.....	...	0.005 gm. atropine sulphate without effect.
34 0	.....	...	Heart stops in diastole; responds to irritation.

FIG. 9.



Time 25′-30″. 1 — + = injection of 0.004 gm. digitalin.
Animal had previously received 0.026 gm. digitalin.

TABLE XIII.—Bock's Method. Digitalin. Dog, weight 9.6 kilos.

Time.	Rate of pulse.	Height of pulse.	
Beginning	102	30–40	
0′ 10″	.....	...	Inject 0.004 gm. digitalin.
1 30	.....	...	Inject 0.004 gm. digitalin.
2 30	84	46–64	
3 30	.....	...	Inject 0.004 gm. digitalin.
5 0 }	.....	...	Inject 0.016 gm. digitalin in four doses.
7 20 }			
8 0	72	36–54	Experiment ended.

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MULTILOCULAR CYSTOMA OF THE PANCREAS.

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Numerous cases of cystic tumors of the pancreas have been reported of late years, especially in consequence of the attention which surgeons have directed to lesions of the abdominal viscera. A critical review of the literature of the subject, however, makes it evident that the term pancreatic cyst has been used to indicate lesions differing in etiology, clinical characteristics, and in the results of treatment. Virchow (*Die Krankhaften Geschwülste*, 1863, i. 276) describes two separate varieties under the term *ranula pancreatica*. In the one the entire duct is widened and an ordinary rosary-like dilatation occurs; in the other the duct becomes dilated into a cyst, the contents of which may be slimy, hemorrhagic, or even calculous material.

Nearly twenty-five years later (*Berl. klin. Woch.*, 1887, xxiv. 248) he finds it no longer easy, especially when the cysts are large, to discriminate between the varieties of cystic tumor which may occur in the vicinity of the pancreas. He looks forward to the time, however, when the method of origin of the larger cysts may become more clearly established.

One of the most important contributions to the differentiation of the large cysts in the region of the pancreas was made by Jordan Lloyd (*Brit. Med. Journ.*, 1892, ii. 1051), when he maintained that such cysts might occur in consequence of an injury to this gland as a result of which the wall of the lesser omental sac becomes inflamed and an accumulation of liquid exudation is retained within its cavity. The simultaneous laceration of the pancreas permits the specific secretion of the gland to be mingled with the serous exudation of the omental bursitis.

Occasional instances of multilocular cystic tumors of the pancreas have been reported and have been described as simulating in gross appearances and in structural characteristics the multilocular cystoma of the ovary. Bozeman (*New York Med. Journ.*, 1882, xxi. 46), for instance, removed from the abdomen of a woman, aged forty-one years, a cystic tumor which Garrigues (*Med. Rec.*, 1882, xxi. 286) subsequently described. It consisted of a principal cyst holding two and a half gallons of brown liquid. The wall was trabeculated, the partitions contained large holes, and it bore several secondary cysts of the size of small hen's eggs. The walls were lined with cylindrical or polygonal epithelium, and the hardened section showed that the formation of the secondary cysts took place as in an ovarian cyst. The patient of Riedel (*Arch. f. klin. Chir.*, 1885, xxii. 994), a woman, forty-five years

old, had a tumor in the upper abdomen for nine years, at first not producing any symptoms. In the last year and a half it had increased so rapidly in size that the entire abdomen was filled with a fluctuating tumor thought to be of ovarian origin. Laparotomy was performed, and the cyst was punctured; ten litres of brown fluid escaped, and the tumor was removed. Death occurred four days later. The cysts had an adenoid projection from the wall, several globular spaces communicated directly with the interior, the spaces being lined with cylindrical epithelium, and others had papillary elevations, as in ovarian cystoma. Paltauf examined the body of a female patient of Selzer, aged forty-two years (*Zeitschr. f. Heilk.*, 1886, vii. 19). Death was due to cancer of the breast, but he found a tumor twice the size of a man's fist apparently continuous with the pancreas. Its contents were a thick, slimy, grayish-brown fluid. From the anterior and lower portions of the cyst projected two globular, lobulated masses, the one as large as an apple, the other the size of an egg. They were separated from the main cavity by widely perforated septa, and were composed of an aggregation of smaller cysts. The walls were lined with cylindrical epithelium, and the pancreatic duct was found within the gland.

In Kuhnast's case (*Inaug. Diss.*, Breslau, 1887, 77), a man of fifty-one years, the body of the pancreas was found after death to be made up of cysts, one as large as a medium sized apple. All the cysts were filled with blood in various stages of metamorphosis. Almost the entire gland was transformed into fibrous tissue and the dilated duct was to be traced here and there through the cystic portion.

The case reported by Martin (Virchow's *Arch.*, 1890, cxx. 230) perhaps belongs in the same series. He successfully removed from the region of the pancreas of a woman, fifty years old, a cystic tumor which filled the entire abdomen. It had first been observed when she was twenty-one years of age, and then was the size of an egg. When the patient was thirty-four years old the tumor was as large as a man's head and was thought to be of ovarian origin. An exploratory laparotomy at this time showed the growth to be behind the transverse colon, and the wound was closed. At the final operation fifteen litres of a thick, brown fluid escaped from the cyst, which was isolated except at one end, where it was tied and cut away, leaving a stump about two fingers' thick. A portion of the wall contained a large number of cysts varying in size from that of a hazel-nut to a goose egg. All were lined with cylindrical epithelium, and no pancreatic duct was found.

Gussenbauer (*Prag. med. Woch.*, 1891, xvi. 365) drained a cyst in the region of the pancreas of a woman, twenty-eight years of age. The tumor was first noticed two and a half years before the operation. It then was as large as a fist, but within the last six months had rapidly increased in size until it was as large as a man's head. Several months

after the operation the patient died of phthisis, and Chiari made the post-mortem examination. He found a fistula extending from the abdominal incision to the pancreas, and the left half of the latter was replaced by a collection of cysts, the largest the size of a hen's egg. The smaller cavities were lined with a cylindrical epithelium. The pancreatic duct was opened from the duodenum to the cysts.

Thiroloix and du Pasquier (*Bull. de la Soc. Anat.*, 1892, lxvii. 310) found nearly the whole pancreas of an elderly woman transformed into a mast of cysts—the largest the size of a hen's egg, the smallest less than the size of pease, the whole forming a tumor twice as large as a fist. There was no constriction of the duct of Wirsung.

Cibert (*Gaz. des Hôp.*, 1896, lxix. 347) reports the results of his examination of a cystic tumor successfully removed by Poncet from a woman, twenty-six years old. The growth first was noticed six years before the operation, and increased slowly for four years. Just before the operation it was apparently of the size of the head of an adult. A large cyst was found, in the wall of which were smaller cysts no larger than hazel-nuts. These were lined with cylindrical epithelium, and the wall of the main cyst was traversed by long ridges enclosing communicating spaces.

The above series include all the cases of benign multilocular cysts of probable pancreatic origin I have been able to collect. It is noteworthy that all, with but one exception, have occurred in women; that, as a rule, the growths have existed for a number of years without much change or proving a cause of disturbance; and that rapid increase in size is usually the result of the formation of a single large cyst.

The walls were lined with cylindrical epithelium, and the comparison between them and the ovarian cyst was often made. The statement of the microscopical appearances, however, is not sufficiently detailed to convince the reader that these multilocular cysts were other than retention cysts proceeding from the smaller branches of the duct of Wirsung.

The following case is reported for the purpose of confirming the view that a multilocular cystic tumor, presumably of pancreatic origin, may occur in the region of the pancreas, and belong to the group of proliferating cysts:

Mr. ——, thirty-six years of age, born in Maine, a carpenter and builder, was sent to me October 23, 1899, by Dr. C. D. McCarthy, of Malden, to whom he had been referred by Dr. Tenney, of the same city. There was no evident hereditary predisposition to disease, and the previous health had been excellent, there having been no serious illness since boyhood, when pneumonia had occurred. Syphilis was denied. He was temperate in the use of alcohol and a total abstainer from tobacco. Tea and coffee were used freely, and he was in the habit of drinking two or three glasses of water at his meals.

In the spring of 1899 he was in his usual good health, but in July he

began to complain of a constant dull pain in the left lumbar region, and extending into the dorsal region. It was worse when lying down at night, but was less discomforting when he lay upon his back. The pain gradually increased in severity, until at the end of two or three months it ceased, after the application of tincture of iodine for three or four days. Within the past month he has noticed in the left hypochondrium a swelling, which has increased a third in size during this time.

Throughout his illness he has not been obliged to restrict his diet, and the appetite has been good. During the past month it has been excessive, and there has been also marked thirst. Immediately after eating the food would seem like a weight in the stomach, and there would arise a sense of exhaustion, lasting for a few minutes, or even for a half-hour. More or less belching of gas would occur, a rumbling in the abdomen was frequently to be heard, and peristalsis in the epigastrium was occasionally to be seen. Of late he has had nausea at times, although vomiting is rare. The bowels have been constipated, but the dejections are not unnatural in appearance.

In the past week or two there have been attacks of palpitation, sometimes relieved by the expulsion of gas. During the same period he has felt faint and has looked pale for a while two or three times daily, and has suffered more or less from dull pain in the temples. He has no cough, but is somewhat short-breathed on ascending an elevation. His breath at times smells queerly.

During the past month he has been obliged to micturate six or seven times during the night, and then passes over two quarts of urine, although not more than a pint in the daytime. There is nothing abnormal in the appearance of this secretion. The skin has been dry throughout the illness, although during the summer months he would sweat at night. He has gained five or ten pounds in weight, but has lost so much strength that he has ceased work on this account. His legs easily tire, but his feet do not swell.

On physical examination the face was pale; temperature, 99° F.; pulse, 88; respirations, 20. The heart and lungs were negative, with the exception of the presence of a systolic murmur at the base and apex of the heart. The urine was 1044, alkaline, with a slight trace of albumin, but no sugar. The examination of the blood showed 4,912,000 red corpuscles, 10,000 leucocytes, and 70 per cent. of hæmoglobin.

The epigastrium and left hypochondrium were swollen and tense from the presence of a rounded resistant tumor extending downward and backward to the vicinity of the left twelfth dorsal vertebra, thence forward three finger-breadths above the crest of the ilium toward the median line. The upper border as determined by dulness on percussion was as high as the left nipple. The lower border formed a sharply defined rounded surface. The tumor was elastic, of doubtful mobility, and presented a rounded prominence from the upper just below the left lower costal cartilage in the mammillary line. A wave was to be recognized in the left portion of the tumor. The position of the mass behind the stomach was indicated by the overlying tympany in the upper epigastrium, with easy upward displacement of the gas, and by the ready production of a splashing sound in front of the upper portion of the tumor.

The patient was sent to the Massachusetts General Hospital for further observation. October 30, 1899, ten grammes of glucose were given

in divided doses, but no sugar was to be found in the urine subsequently passed. After salol was taken no urine was voided for six hours; the specimen then examined gave the reaction characteristic of the presence of salicylic acid.

A diagnosis of cyst of the pancreas was made, and the patient was transferred to Dr. M. H. Richardson's ward for surgical treatment.

November 7, 1899. An incision seven inches long was made over the tumor, two inches to the left and parallel with the median line. The tumor was found to occupy the region of the lesser omental cavity. A trocar was pushed through the wall and a considerable quantity of reddish-brown fluid escaped. It was apparent that the cyst was multilocular, the separate cysts, some of which were nearly as large as the fist, not being intercommunicable. The intervening septa were torn through, as much of the contents removed as possible, and the sac was then sepa-

rated from the surrounding parts and detached. Diseased portions of what was supposed to be the pancreas, but having a malignant look, were removed with the tumor. Six weeks later the patient was discharged relieved. At the site of the wound was a sinus at least two inches deep, from which a slight discharge escaped into the dressings.

A portion of the liquid contents of the tumor was examined in the laboratory of Prof. E. S. Wood by his assistant, Mr. H. C. Smith, with the following result:

Quantity, 250 c.c.; color, dark brown; sp. gr., 1022; reaction, alkaline. Considerable free blood present, but no pancreatic ferment.

Solids	7 32 per cent.
Urea	0 18 "
Albumin	1 66 "
Ash	0.81 "
Chlorine	0.32 "
NaCl.	0 53 "

Dr. W. F. Whitney received the fresh specimen and forwarded the following report:

"Hemorrhagic cystadenoma; a cystic mass the size of a squash, of a dark-red color, indicating extensive hemorrhages, with a very soft necrotic tissue mingled with dark-red fluid. No definite pancreas could be made out, though some of the hemorrhagic masses suggested a piece of the pancreas, and another an infiltrated adrenal gland. A little piece of the tissue was soft, grayish, and rather malignant-looking to the eye."

On microscopic examination of hardened and stained sections, rounded and irregularly sinous cavities of various size were to be seen, some with incomplete septa, others with projecting papilliform growths. Some of the cavities contained granular, fibrillated, or hemorrhagic material; others were filled with papilliform growths grouped in a somewhat irregular manner. The contents were occasionally cellular, the cells being free or clumped, at times in tufts. Many of the cavities were lined with a cylindrical epithelium, which was more or less stunted in the larger cysts. Some of the papilliform growths bore a cylindrical epithelium, while others were covered with cuboid cells. Occasionally the distribution of the epithelial cells suggested the acini of the pancreas, but the normal structure of this gland was not seen in any of the sections examined. The connective tissue between the cysts in places was densely fibrous, while elsewhere it contained numerous cells and was composed of interlacing fibrils, the latter forming a meshwork enclosing a more or less homogeneous intercellular substance. Large and thin-walled bloodvessels were numerous. In places granules of blood-pigment and agglomerated red blood-corpuscles gave evidence of old and recent hemorrhages, while extensive areas of necrosis, in which the structural details were well preserved, were not infrequent. It was in their vicinity particularly that the thin-walled bloodvessels and the hemorrhages predominated.

Although the above-mentioned characteristics prevailed in the sections examined, in a few of the latter a tendency to the atypical growth of epithelioid cells was apparent. The cells were of a cylindrical character, but by no means of a uniform shape, size, and arrangement, and were grouped in a tubular form, but the tubules often were so closely approximated as to present an irregularly alveolate appearance.

The tumor, from its histological appearances, thus is to be regarded as essentially a multilocular cystoma, but on the border line between a proliferating cystoma or cystadenoma and a cystomatous carcinoma, a distinction which the subsequent history of the patient may be expected to make clear.

Combinations of cystoma and carcinoma in pancreatic tumors have been reported in rare instances. Hartmann (*Cong. Franc. de Chir.*, 1881, 618) records the case of a woman, fifty-three years old, who had suffered from digestive disturbances for some time, but within three months had rapidly become emaciated and enfeebled. In this period there were abdominal pains, and a tumor appeared, seemingly as large as the two fists. Laparotomy was performed, and at the operation 200 grammes of brown, chocolate-like fluid were removed from the growth, which lay behind the stomach, and its cavity was drained. Death oc-

curred some six weeks after the operation. At the autopsy the entire body and tail of the pancreas were found to form a polycystic mass, through which the pancreatic duct could be followed. Cancerous nodules were found in the liver, and Gilbert, who examined the cysts, regarded them as representing a cystic epithelioma, with the new formation of glandular cul-de-sacs presenting a cystic dilatation.

Reference is made in the article just mentioned to a work published by Hanot and Gilbert (*Etudes sur les Maladies du Foie*, Paris, 1888), where a case is referred to in which a series of cysts of various dimensions were found in the pancreas. The tumor was generalized in the liver, and Gilbert regarded it as a tubular pancreatic epithelioma.

A CRITICAL SUMMARY OF THE LITERATURE

ON THE

INOCULABILITY OF CARCINOMA.

By Joseph Sailer, M.D.

Perhaps the most common experiment that has been made for the purpose of elucidating the true nature of malignant tumors is the inoculation of fragments of them into other living beings. The number of experiments of this nature is now very considerable, and the results are astoundingly at variance. They may be divided into certain general groups, depending in part upon the method of procedure, in part upon the animals used as subjects. In order that such experiments should be decisive it is necessary that certain precautions should be observed which in a general way resemble the rules laid down by Koch for the purpose of determining the relation of microorganisms to disease. First, the nature of the original tumor should be carefully determined by microscopical examination. Second, the inoculation should be made under the most rigid aseptic precautions. The failure to observe this has caused at least one investigator to obtain results that are absolutely valueless. Third, the animal should be kept a sufficient length of time under observation. The maximum has never been determined, but it is conceivable that months or even years may elapse before the tumor develops. Fourth, if a tumor does develop its nature should be carefully determined by microscopical examination, and if it is similar to the original tumor it should be possible to continue the inoculations in other animals. It is, of course, desirable at present, when the parasitic theory of carcinoma is so widely accepted, to make all possible efforts to determine the existence of the

bodies that have been supposed to be parasites, and that have been found in tumors, and to make cultures from the original tumor and from the tumor that develops at the site of inoculation. It is advisable also, in view of the possible spontaneous occurrence of tumors in the lower animals, to keep always a certain number of controls and to make inoculations in sufficient number of animals to eliminate as far as possible any accidental development. These conditions have not been by any means carefully observed. The great majority of investigators have been satisfied by the mere injection or implantation of fragments of supposed carcinoma obtained from a human being, often not controlled by microscopical investigation, and then at the expiration of a limited period of time the animals have been killed and examined in order to see whether any tumor growth has taken place. Of course, under these circumstances negative evidence is practically valueless.

The experiments may be divided into the following groups: inoculation of the lower animals with tumors from other animals or from human beings; inoculation of human beings either with fragments of tumor from some other part of the body or with tumors from other human beings; finally, mediate inoculation with portions of tumors kept for some time outside the body or with cultures obtained from tumors.

Among the earliest experiments of this group were those of Novinsky (quoted by Geissler), who removed an alveolar epithelial tumor from the nose of a dog, and made with it forty-two inoculations into the skin of other dogs. Sometimes he inoculated it into places where the skin was irritated; in others where it was normal. In two of the latter situations tumors subsequently developed that upon histological examination were found to have the same structure as the original tumor of the dog's nose. Some very important experiments were reported by Wehr[1] and by Hanau.[2] Wehr took portions of tumors of the prepuce of dogs or of the mucous membrane of the vestibula and inoculated them into the subcutaneous connective tissue of twenty-six other dogs. Twenty-four nodules were obtained, five of which were examined microscopically, and in one case the tumors grew progressively until the death of the animal, which was brought about by rupture of the bladder as the result of the compression of the urethra by the tumor mass. The whole pelvic cavity in this instance was infiltrated, and metastases were found in other parts of the body. The microscopical examination is not recorded. Hanau inoculated fragments from the cancroids of the vulva of a rat into the tunica vaginalis testis of other rats. One died at the end of seven weeks, after having developed diffuse carcinoma of

[1] Langenbeck's Archiv, 1889, vol. xxxix. p. 226.

[2] Ibid., p. 678.

the peritoneum. A second rat was killed at the end of eight weeks, and two tumors were found—one in the adrenal body and the other in the gubernaculum. A fragment of tumor from the second rat was inoculated into a third rat, which was killed three months later. At the point of inoculation there was considerable tumorous infiltration, and the whole of the peritoneum showed extensive metastases. Hanau regarded his experiments as completely successful, and they certainly fulfilled the conditions that were laid down at the beginning of this article. Nevertheless, on subsequent consideration[1] he became convinced that they did not necessarily prove the infectious origin of the cancer, but simply that the transplanted epithelial cells were capable of proliferating in their new environment, just as the transplanted epithelial cells of a skin graft can proliferate if placed in the midst of granulated tissue. Some years later Jenny[2] published the results of a careful histological examination of the various tumors that had resulted from these inoculations, which were found to consist of typical cancerous masses composed chiefly of epithelium that had undergone to a considerable extent horny degeneration and of cancerous stroma, proving that the tumors produced by the inoculations practised by Hanau were undoubtedly true cancers. Among the most valuable experiments of this type are those of Moreau,[3] who found in a mouse that he had at his laboratory for some time a small tumor under the right axilla. This was removed and in part kept for histological examination, in part triturated with sterile normal salt solution. With this ten white mice were injected, and two died without lesions. The others in eight months developed tumors similar to the original. Another group of ten were inoculated with these, and in five months all had developed tumors. A group of mice born of parents suffering with tumors were also inoculated, and some of them developed masses as large as themselves. Other mice were fed with the tumor material, and developed tumors after some months. All these tumors, apparently developed in the connective tissue, were of an alveolar structure and contained epithelium that infiltrated the surrounding tissues. General metastasis rarely occurred unless some traumatism had been applied to the edge of the tumor. Other animals were also inoculated, but were not as susceptible as the white mice. Experiments performed with cancers obtained from human beings were negative. It was impossible to obtain cultures from the tumors by any method. Moreau concludes, and it seems impossible to contradict him, that the cylindrical epitheliomas of white mice are inoculable into other animals of the same species; that heredity apparently plays a considerable rôle in increasing the susceptibility of

[1] Fortschr. der Medicin, 1889, vol. vii., No. 9.
[2] Archiv f. klin. Chir., 1896, vol. li. p. 269.
[3] Archiv de Med. Exper. et d'Anat. Path., 1894, vol. vi. p. 677.

the animals to the tumors, and also that the growth of the neoplasm is greatly increased by gestation. If the tumors are transferred to other animals of different species they apparently lose their virulence and inoculability.

Less satisfactory, because the experiment was not carried as far, is the work of Eiselberg.[1] He removed a fragment from a spindle-cell fibrosarcoma of the shoulder of a white mouse and inoculated it into the peritoneal cavities of two half-grown rats, in one of which the tumor continued to develop until it caused death at the expiration of five months. The tumor had the same histological characteristics as the primary growth. Pfeiffer (quoted by Geissler) has transmitted a melanotic tumor from one mouse to another.

Shattock and Ballance,[2] in the course of a series of experiments, transplanted fragments of carcinoma from one dog to others, but the results were always negative. Trasbot[3] has transferred fragments of carcinoma from one dog into others, using every known method of inoculation. In one instance a small mass developed at the end of six weeks, but later disappeared completely.

Duplay and Cazin[4] have made a great number of experiments, inoculating rats, guinea-pigs, rabbits, and dogs with fragments of carcinoma and sarcoma obtained from tumors occurring spontaneously in dogs. Inoculations were made subcutaneously, intraperitoneally, and intravenously, but the results were uniformly negative. In a subsequent communication,[5] in which they referred to these experiments, they add that in one instance a tumor resembling in structure an inflammatory growth that had been found in the mucous membrane of the vagina of a dog was inoculated into a number of other dogs. In one of these, at the expiration of ten months, there was proliferation at the site of inoculation, and metastatic tumors of a distinctly epithelial structure in the testicles. In none of the others, however, were there any evidences of metastases. This case is, of course, extremely doubtful, and the authors, in another paper,[6] in a careful review of the subject, reach the conclusion that there is not sufficient evidence at present to prove that cancerous and sarcomatous tumors are contagious, and that although it is not unlikely that they are infectious, their infectious nature is not at present understood. Geissler[7] inoculated two dogs with fragments of papillomatous tumors of the penis found in dogs. In one a tumor appeared in three weeks at the site of inoculation that had the same structure as the original, but ultimately disappeared; in the other

[1] Wien. klin. Woch., 3d Jahrgang, 1890, No. 27, p. 927.
[2] British Medical Journal, 1891, No. 1576.
[3] Centralb. f. allg. Path. u. path. Anat., vol. v. p. 394.
[4] Semaine Médicale, 1892, p. 61.
[5] Centralb. f. allg. Path. u. path. Anat., 1894, vol. v.
[6] Semaine Médicale, 1893, p. 329.
[7] Verhandl. der deutschen Gesellsch. f. Chirurgie, 24th Congress, Berlin, 1895, p. 87.

tumors appeared in three places at the end of five weeks. The animal became cachectic and died in eight months, and numerous metastatic nodules were found, and with them a third dog was successfully inoculated. Geissler does not consider the tumor a typical carcinoma. In the discussion that followed Geissler's report Hansemann stated that he believed the tumor was a mixture of sarcoma and granulation tissue, and Israel agreed that it was not carcinomatous. Rosenbach related an instance of successful transmission of sarcoma from one rat to another. Smith and Washburn[1] describe an infectious papilloma occurring in dogs which apparently attacks the epithelium of the sexual organs. They observed a number of cases of direct contagion, and in two cases made successful experimental inoculations. In the second of these the tumor subsequently atrophied. The authors regard these tumors as similar to those described by Wehr, Duplay and Cazin, and Geissler. Finally, with an allied type of tumor, the endothelioma that were found in three members of the same litter of white mice Eberth and Spude[2] made a series of transplantations into other white mice, using various methods of inoculation, but the results were invariably negative.

The most obvious experiments, of course, are those which consist of inoculating the lower animals with fragments of carcinoma removed from human beings. According to Hauser, if carcinoma is an infectious disease, such inoculations should be successful, because we know that certain of the lower animals, particularly the dog and rat, are frequently affected by cancerous growths. Among the successful early essays in this direction were those of Goujon (quoted by Geissler), who succeeded in producing a tumor in a rat as a result of inoculation of a fragment of carcinoma. The microscopical control of this tumor is not given. Klemke (quoted by Geissler) has also obtained a positive result in a horse by inoculating it with some of the scrapings of a melanotic carcinoma. It is, of course, questionable whether the tumor was not really a sarcoma.

Among the more modern experiments in this direction that were successful may be mentioned those of Power,[3] who inoculated fragments of carcinomatous Paget's disease upon mucous surfaces that had been irritated for a long time. Fragments from Paget's disease gave, as he states, interesting results. The communication is brief, and there are no satisfactory details. But later[4] he stated that he found in the proliferations the parasites of Ruffer—a very unsatisfactory proof of tumor formation. The experiments of Adamkiewicz[5] consisted of

[1] Journal of Pathology and Bacteriology, January, 1898, vol. v. p. 99.
[2] Virchow's Archiv, 1898, vol. cliii. p. 60.
[3] Journal of Bacteriology, vol. i., No. 6.
[4] British Medical Journal, 1893, vol. iii. p. 830.
[5] Untersuchungen über den Krebs und das Princip seiner Behandlung. Experimentel und klinisch. Wien. and Leipzig, 1898.

implanting various tissues in different regions of animals. Fragments of carcinoma placed in the brain produced a characteristic reaction that he ascribes to an intense specialized intoxication. The symptoms appeared after two or three days, when the animals became sluggish, suffered from embarrassed respiration, then developed nystagmus and opisthotonos, and died. At the autopsy the brain was pale; there were no signs of inflammation, and cultures made from the tissues remained sterile. Adamkiewicz believes, as a result of these and other experiments, that carcinoma is a true infectious disease, in which the micro-organisms are represented by the so-called epithelial cells. These elaborate a poison—cancroin—that has a special affinity for nervous substances. The experiments were apparently made with reasonable antiseptic precautions. The fact that no cultures were obtained from the brain, if true, is of course of extreme significance. The validity of these experiments was soon tested by men whose statements carry weight. Paltauf,[1] in a review of Adamkiewicz's work, states that he had repeated these experiments with negative results. Geissler[2] inoculated twenty-five rabbits according to Adamkiewicz's method, employing, however, more elaborate aseptic precautions. Even with these he occasionally got positive results always due to septic infection; otherwise the animals showed absolutely no symptoms, although kept under observation for many months. In those that were killed for study the fragments of carcinoma, although tolerably well preserved, exhibited no tendency to proliferate, and produced exceedingly little reaction in the surrounding nervous tissue. Kopfstein[3] implanted fragments of carcinoma into the brains of eight rabbits, and Kinscherf and Bartsch[4] inoculated twelve rabbits with fragments of carcinoma. These were removed under the most careful antiseptic precautions and embedded in the brain-substance of the animals. Their results were identical with those of Geissler, and it seems reasonable, in view of the unanimity of the negative testimony, to disregard entirely the implantation experiments upon which Adamkiewicz bases his theory.

Langenbeck (quoted by Hahn) has succeeded in producing carcinoma of the lung by injecting some cancer juice mixed with blood-serum into the jugular vein of a dog. The nodules were found when the animal was killed two months after the inoculation. Lebert and Toller (quoted by Hahn) injected an emulsion of mammary carcinoma into the jugular vein of a dog, and fourteen days later found some nodules on the pericardium. The rapidity with which the secondary growth occurred was against its cancerous nature. Lanz[5] implanted a fragment from a col-

[1] Wien. klin. Woch., 1893, No. 37.

[2] Arbeiten aus der chirurg. Klinik der königlichen Universität zu Berlin, 8te Thiel., Berlin, 1891, p. 70.

[3] Wien. med. Woch., 1893, p. 1252.

[4] Beiträge zur klin. Chir., 1894, vol. xi. p. 321.

[5] Deutsche medicinische Wochenschrift, 1899, vol. xxv. p. 313.

loid struma into the thyroid gland of a dog, and later the animal died with symptoms of thyroidism, and a fragment of a melanotic sarcoma into a guinea-pig, causing apparently general melanosis of the tissues without tumor formation. On the other hand, numerous inoculations of human carcinomas into animals were without result, for, although the fragments sometimes increased in size for a time, they always ultimately were absorbed. Inoculations of sarcoma and keloid were entirely negative.

Bambeke[1] reported that Firket had made successful inoculations with fragments of human sarcoma into five rats, all of which died at the expiration of five weeks as a result of the development of tumors. Cultures from these tumors remained sterile. The rapidity with which death was caused is strongly against the accuracy of these experiments and the histological examinations of the secondary tumors are not reported. Francotte and Rechter, whose work was reported by Crocq,[2] inoculated three mice behind the shoulder with cancer juice. Later the foreleg on that side sloughed away as the result of a process of dry gangrene, and there was some tumor formation, fibrous in nature, in the scar. This they regard as cancerous. Crocq is much more skeptical, particularly as the tumor growth was always scirrhous in character, no matter what form of cancer had been used in making the inoculation, and it seems clear that these results cannot be regarded seriously.

Mayet[3] has macerated tissue from human beings in glycerin, and with this made repeated inoculations into rats. After some time cachexia developed and the animals died, sometimes with and sometimes without tumor formation. Fragments of carcinoma embedded in tissues were absorbed without lesion. It is singular that so few investigators have used the glycerin emulsions.

The negative evidence, on the other hand, is tremendous. Weigert (quoted by Kubassoff) has made numerous implantations into the muscular tissue, into the peritoneal cavity, and into the subcutaneous tissues of dogs and rabbits with fragments of carcinoma, and the only reaction that was observed was identical with that found when normal tissue was implanted. These experiments are probably the same as those reported by Senger,[4] who inoculated a number of mice, rabbits, and dogs either intraperitoneally or intramuscularly with fragments of carcinoma. The results were always practically identical, and he therefore describes only a single case. The fragment first increased in size for some time, then gradually diminished, and finally disappeared completely. Histologically, fragments examined at various stages of the process showed central necrosis and atrophy of the cells toward the periphery and invasion of the periphery by fully formed bloodvessels—

[1] Semaine Médicale, 1893, p. 8.
[2] Ibid., 1892, p. 482.
[3] Ibid., 1893, p. 283.
[4] Berlin. klin. Wochenschrift, March 5, 1888, p. 185.

that is to say, the ordinary signs of necrosis and absorption. He was unable to obtain any form of micro-organism. Fischel[1] inoculated twenty-three rats intravenously, intraperitoneally, and subcutaneously with sterile fragments of various types of carcinoma and of a small-celled and of a melanotic sarcoma. The fragments all underwent necrosis, and in spite of very careful histological examination no trace of proliferation could be observed. Nevertheless, Fischel does not believe that these results necessarily indicate that carcinomas and sarcomas are not infectious, but only that when transplanted into animals of another species the carcinomatous tissue fails to develop. Wickham[2] inoculated a number of species of rodents with epithelial cells containing parasites from cases of carcinoma and of Paget's disease, but the results were invariably negative. Klebs[3] undertook a series of transplantation experiments with fragments of carcinoma from human beings into white rats, and although the fragments were absorbed, thus giving an opportunity for the liberation of any micro-organisms that may have existed in them, the results were invariably negative. Shattock and Ballance[4] have inoculated monkeys, cats, rats, and sheep with fragments of carcinomas and sarcomas. These were absorbed or surrounded by the products of inflammation, and although some of the animals were kept alive for 700 days, absolutely no tumor formation occurred. Duplay and Cazin[5] have performed about 120 experiments upon the transplantation of carcinoma from human beings to the lower animals, using all known methods of inoculation, and failed invariably. Trasbot[6] for thirty years performed numerous experiments, injecting carcinomatous substances and material into animals, usually dogs, and in all cases except one without result. In this a small tumor developed in the course of a few weeks at the site of inoculation, and then gradually atrophied. Paulowski[7] has also performed a series of experiments upon the lower animals, such as frogs, rabbits, and dogs, with negative results. D'Anna[8] has also had negative results from inoculation experiments. Plimmer[9] is convinced, as a result of numerous experiments, that carcinoma cannot be reproduced in the lower animals. Senn[10] has inoculated dogs with fragments of carcinoma and sarcoma in various ways, but the results were always negative. Török and Tomassoli,[11] although they believe molluscum contagiosum to be a contagious disease, have been unable to produce it by inoculation into the lower animals.

[1] Fortschr. der Med., 1892, p. 1.
[2] Archiv de Med. Exper. et d'Anat. Path., 1890, vol. xi. p. 46.
[3] Allgemeine Pathologie, Vienna. 1889.
[4] British Medical Journal, April, 1891, No. 1576, p. 565.
[5] Centralblatt f. allg. Path., etc., vol. v. p. 394.
[6] Ibid. [7] Ibid. [8] Ibid.
[9] British Medical Journal, 1899, vol. ii. p. 920.
[10] Pathology and Treatment of Tumors, Philadelphia, 1900, p. 240.
[11] Monatschrift f. prakt. Dermatol., 1890, vol. xi. p. 149.

Metschnikoff,[1] some time ago, suggested that perhaps the cancer parasite was obliged to pass through some portion of its life's cycle outside of the living host, and that, therefore, we should endeavor to cultivate it outside the body for a short time before inoculating it. This experiment has been done a number of times. Usually some micro-organism has been obtained which was secured in pure culture, and with it an inoculation performed. This branch of the subject hardly comes under the category of inoculation experiments, but a few of the results obtained by recent workers may be mentioned. Pease[2] gave an intravenous injection into a guinea-pig of peritoneal fluid from a case of colloid cancer of the peritoneum. This fluid he had withdrawn and kept for ten days in an incubator, and three and one-half weeks after the injection the guinea-pig was killed and a nodule of adenocarcinoma found in the lung. A considerable number of other experiments were negative. Sanquirco[3] isolated the bacillus of Scheuerlen from several carcinoma, and inoculated pure cultures into the lower animals, producing sometimes septicæmia and sometimes local infection. Kubassoff[4] describes a bacillus obtained from a gastric carcinoma that caused tumors in animals when inoculated into or when fed to them. In another series of experiments he obtained the same micro-organism from cancers from three young persons, and they still produced the same results. Unfortunately, no notes are given of the latter group of experiments. The paper is written so carelessly, and, considering the extraordinary importance of the results achieved, the details are so meagre and unsatisfactory, that in the absence of further reports or of any confirmatory evidence whatever, it can, I think, be entirely disregarded. Schoebe contends that the course of the disease in the inoculated animals does not resemble that of adenocarcinoma. More careful work was done by Curtis,[5] who obtained a yeast from a subcutaneous tumefaction in a man, and was able to produce some infectious growths in the lower animals. After exact histological examinations of these masses he reached the conclusion that they were not tumors, but simply local foci of reactive inflammation and masses of the micro-organisms. Interesting results were also obtained by Mafucci and Sirleo,[6] who obtained blastomycetes from the body of a marasmic guinea-pig. Inoculated into the lower animals it caused an epitheliomatous ulcer of the skin, with swelling of the lymph-glands. Subsequently the tumor disappeared, but when the animals died miliary nodules were found in the lungs. If large doses were injected there was proliferation of cells of the lymph spaces (endothelioma ?).

Sanfelice[7] describes a blastomycete that he obtained from fruit juices.

[1] Ann. de l'Ins. Pasteur, 1893.
[2] Public Health Papers and Reports, 1900, vol. xxv.
[3] La Riforma Medica, Anno. v., No. 46, p. 272.
[4] Wien. med. Presse, July 20, 1890, p. 1145.
[5] Annales de l'Institute Pasteur, 1896, No. 8.
[6] Centralblatt f. allg. Path., etc., 1895. p. 305.
[7] Centralblatt f. Bakt. u. Parasitenk. 1895, vol. xvii. p. 625, and 1898, vol. xxiv. p. 155.

He inoculated three dogs and a cock with this, and it produced tumor-like masses, from which he was unable to obtain the micro-organism in cultures. In one case pus from one of the dogs caused tumor formation in one of four others. Lubarsch[1] has repeated these experiments with two cultures of blastomycetes, one obtained from an epithelioma of the lip, the other from Sanfelice through Kral's laboratory. He was unable to produce tumors of any character in guinea-pigs or rabbits. Busse[2] also criticises Sanfelice's results, chiefly because the nature of the tumors is not clear and the micro-organisms were not obtained from them.[3]

Plimmer[4] has recently been able to cultivate the organism described by Ruffer upon a bouillon made of cancer tissue to which 2 per cent. of glucose and 1 per cent. of tartaric acid were added. This belongs to the yeast group, and inoculations produce a distinct proliferation of endothelium upon the serous surfaces of rabbits. In another article[5] he states that he regards the organism as a protozoon, and describes his inoculations, which in one series of animals caused death in periods of thirteen to twenty days, with the production of small nodules consisting of the proliferating endothelial cells in the serious membrane and in the lung. Up to the present proliferation of the epithelial cells was not observed. Plimmer concludes that certain undoubted parasitic intracellular bodies occur in carcinomas that can be cultivated outside of the body, and will produce tumor formation when inoculated into animals.

Finally comes the group of experiments in which human beings themselves are the subjects. Allebert (quoted by Geissler[6]) inoculated himself and four others with cancer juice, but caused only temporary inflammation. Wickham[7] inoculated himself with tissue from a case of Paget's disease, but the result was negative. Of course, it has been known for some time that carcinomas might develop in tissues or on raw surfaces from which cancer juice had flowed in the course of operation, and Remcke[8] observed nodules develop in the wall of the abdomen in the line of puncture made for the withdrawal of ascetic fluid produced by a carcinoma of the peritoneum; and Bergmann (quoted by Hahn) has reported a case of cancer of the lip acquired through contact with cancer of the tongue. Williams (quoted by Kubassoff) has observed a case of inoculation by cancer from one leg to another. Rarer and less well authenticated cases are those in which contagion takes place from one individual to another. Among the most inter-

[1] Zur Lehre von den Geschwulsten und Infektionskrankheiten, Wiesbaden, 1899, p. 313.

[2] Ergebnisse der allg. Path. u. path. Anat., Lubarsch und Ostertag, fifth year, Wiesbaden, 1900, p. 401.

[3] It is hardly fair to Sanfelice to attempt to make a summary of his work from the above articles. His publications on the subject are very numerous.

[4] British Medical Journal, 1899, vol. i. p. 748.

[5] The Practitioner, 1899, vol. x. p 430.

[6] Loc. cit.

[7] Loc. cit.

[8] Virchow's Archiv, vol. li.

esting experiments of this nature are those reported by Hahn and Cornil. Hahn[1] removed fragments from a disseminated carcinoma of the skin and placed them on healthy skin in the same patient. Eleven weeks later these skin grafts had reached the size of cherries. Histologically they resembled the original tumor in all respects. Hahn believes that the infection of healthy skin during operation is possible. Cornil[2] reported the experiments of a physician whose name he withheld. This surgeon, while amputating a tumor of the breast, inserted a fragment of the tumor into the opposite breast. Two months later a tumor the size of an almond was removed. Cornil examined both specimens, and found that they were identical and consisted of alveolar sarcoma (*sarcome fasciculé*). He believes that there is no doubt that the second tumor arose from the fragments inoculated. The same surgeon performed this experiment in another case, and the clinical course resembled that of the first. Unfortunately, the patient refused to submit to a second operation, and left the hospital with a tumor of the breast of considerable size. The primary tumor was a tubular epithelioma. Of course, it is possible in both these instances that the patients were predisposed to tumor formation. Nevertheless, they demonstrate that fragments of tumor can become incorporated and continue to grow in healthy tissues. Pick[3] inoculated the contents of molluscum contagiosum upon a nine-year-old girl and an eleven-year-old boy. At the end of ten weeks a small characteristic lesion appeared in one of the spots of inoculation, and subsequently numerous others also developed. Török and Tomassoli,[4] however, were unable to reproduce this disease by inoculations into human beings. Lanz[5] has succeeded in inoculating a group of warts in the form of a J upon the back of his gardener's hand.

In conclusion, I wish to mention two remarkable methods that have been suggested, and one of which has been employed in order to produce cancer. V. Kahlden[6] states that Klebs has suggested that fragments of the fœtus implanted in the placenta might give rise to a malignant tumor—that is, to a diffuse carcinoma of the uterus. V. Kahlden does not believe that this would be the case. Lack,[7] believing that the epithelial cells are the infectious agents of cancer, has scraped the ovary of a healthy rabbit into its peritoneal cavity. Fourteen months later he states that the animal died of ovarian cancer. In another preliminary communication[8] he gives a more complete account of the lesions. Numerous hard, white nodules were found on the mesen-

[1] Berlin. klin. Wochenschrift, May 21, 1888, p. 413.
[2] Semaine Médicale, 1891, p. 259.
[3] Archiv. f. Dermatologie u. Syphilis, 1892, p. 89.
[4] Loc. cit.
[5] Loc. cit.
[6] Centralb. f. allg. Path. u. path Anat., 1891, p. 1.
[7] British Medical Journal, 1899, vol. ii. p. 179.
[8] Journal of Pathology and Bacteriology, August, 1899, vol. vi. p. 154.

tery, pleuræ, and diaphragm; the mediastinum was converted into a tumor mass, and the liver contained nodules and cysts. All the "growths consisted of alveolar spaces lined by one or occasionally more layers of columnar epithelial cells." As, according to MacFadyean, the rabbit is not subject to cancer, Lack believes that the "operation produced the disease." It may not be amiss, in this connection, to mention that Schultz[1] has transplanted ovaries to the peritoneal cavities of male guinea-pigs, and at the end of eleven days observed only a moderate atrophy and no trace of proliferation or tumor-like development. Moreover, Lengemann[2] has made a number of experiments with dislocated tissues and injections of tissues, and Lubarsch[3] has performed the same experiments without obtaining any tumor-like proliferations.

An analysis of the work performed by various investigators in this field leads to some conclusions that may not be wholly without value. The transmission of malignant tumors from one animal to another of the same species appears to be definitely established by the work of Hanau, with its subsequent careful histological control by Jenny, by the work of Eiselberg, and particularly by the elaborate experiments of Moreau. On the other hand, the experiments of Wehr, Duplay and Cazin, Geissler, and Smith and Washburn are inconclusive, for the reason that we are not certain that these authors were using in their experiments true tumors, and not, as seems more likely, a form of infectious granuloma that has not yet been recognized as such. The transmission of tumors to the lower animals from human beings may be regarded as absolutely impossible unless some profound modification in technique or in the preparation of the animals subjected to the experiments shall be devised, and at present there is no reason to believe that any modification with which we are likely to become acquainted in the near future will suffice for this purpose. The results are invariably doubtful; not a single positive experiment has been carried out with precautions regarding the histological nature of the growth and its development in the lower animals that would render it worthy of a moment's consideration. There is no reason to believe that cancer tissue introduced into the lower animals acts in any respect differently from any other tissue introduced into the lower animals. It produces the same effects and suffers the same changes. It is hardly necessary to refer here to the discredited experiments of Adamkiewicz. The effects of mediate inoculation are very doubtful. Certainly none of the bacteria that have been described need be regarded as etiologically associated with cancer. On the other hand, there is apparently slightly more evidence

[1] Centralb. f. allg. Path. u. path. Anat., 1900, vol. xi. p. 200.

[2] Zur Lehre von den Geschwulsten und Infectionskrankheiten von Lubarsch, Wiesbaden, 1899, p. 3 et seq.

[3] Ibid., p. 246 et seq.

to prove that certain blastomycetes can, under favorable circumstances, produce proliferation of the cells with which they may be in contact, but this proliferation is apparently in the majority of cases endothelial and not epithelial in character. It is a curious fact that Sanfelice has not been able to recover his organisms in culture from the tumors that he alleges they have produced, and it is also singular that the organisms found by Sirleo and Mafucci and by Sanfelice were obtained not from tumors, either in human beings or the lower animals, but in one case from a cachectic guinea-pig and in the other from juices of decaying fruit. It was to be expected that the transmission of cancers from one human being to another would be successful in view of the successes of similar transmissions in the lower animals. Aside from the reports of Cornil and of Hahn, however, even this experiment appears to have failed. The negative results, at any rate, at present certainly outweigh the positive results. It is to be noted, moreover, that in the reports of Cornil and of Hahn the tumors were transferred only to other supposedly healthy parts of the same individual. The experiment of Lanz with cutaneous warts was very decisive, but we are still rather doubtful regarding the nature of these growths.

It will perhaps not be out of place to suggest in what direction subsequent investigation upon the subject of the etiology of malignant neoplasm should apparently be pursued. It seems useless to continue inoculating lower animals with fragments of human cancers; it is criminal to use human beings as subjects for these experiments, and we are, therefore, restricted to inoculation experiments with such malignant tumors as may develop spontaneously in the lower animals. These tumors are not uncommon in dogs, and probably are more frequent than is ordinarily supposed in the ordinary laboratory animals. It is urgently necessary that a number of investigators undertake the elucidation of this subject and determine under what conditions and by what methods the transmission of the tumor actually takes place. In regard to mediate inoculation—that is, the study of the tumors with reference to the presence of parasites—it does not seem that at present we are sufficiently familiar with the blastomycetes or with the lesions that they produce in animals to reach any positive conclusion. It is very necessary, therefore, that the blastomycetes be studied from a botanical stand-point, and that the lesions produced be more carefully described. As for coccydia or protozoa, Schaudinn,[1] one of the keenest workers in this field, has recently stated that from a careful examination of sections of one hundred malignant growths in which the so-called cancer parasites were present he was convinced that the growths did not contain any bodies that could be regarded as coccydia or protozoa.

[1] Zoolog. Jahr. Abth. f. Anat. u. Ontolog. der Thieren., 1900, vol. xiii. p. 197.

REVIEWS.

On Neuroma and Neuro-fibromatosis. By Alexis Thomson. Edinburgh: Turnbull & Spears, 1900.

This is an admirable monograph, and may be read with profit by those interested in the fibrous overgrowth in nerves. Thomson has had a remarkable experience in the observation of fifteen cases. He includes under the fibrous proliferation of nerves the multiple neuro-fibromata, the plexiform neuro-fibromata, the cutaneous neuro-fibromata, elephantiasis neuromatosa, the pigmentation of skin associated with neuro-fibromatosis, and secondary malignant neuroma—*i. e.*, sarcomatous transformation in any of the forms of neuro-fibromatosis. This seems to be a perfectly proper classification in the light of recent studies.

It must be borne in mind that the term neuroma when used in the clinical sense is made by some to include tumors of various kinds, whatever their structure may be; the existence of true neuromata, however, Thomson believes, can no longer be denied. These tumors are exceedingly rare, especially if we exclude stump neuromata. The latter are true neuromata, as anyone may convince himself by examining with the microscope a tumor of this character. It is wise to devote a few words to the true neuromata, because many pathologists still question the existence of such growths. Thomson refers to five authenticated cases of true neuromata in which the tumor or tumors were composed of newly-formed ganglion cells and of medullated and non-medullated nerve fibres. In all these cases, with one doubtful exception, the true neuromata were in connection with the sympathetic nervous system. It is noteworthy that these true neuromata do not appear to be combined with any of the forms of neuro-fibromatosis. The five cases referred to by Thomson are those reported by Knauss, Busse, Schmidt, Loretz, and Key. Thomson makes no reference to the disputed cases of true neuromata of the spinal cord in the literature. A few cases of this character have created much contention in regard to the correct interpretation of the findings.

Thomson believes that the circumscribed or solitary tumors growing from the connective tissue of nerves constitute a distinct and separate class of false neuromata. In the opinion of the reviewer this view is not well sustained. While transition forms between the solitary tumor and general neuro-fibromatosis are not incompatible with the differentiation into different classes, they nevertheless weaken this differentiation in proportion to their frequency of occurrence. Again, the discovery of one or more tumors is no evidence whatever that latent growths are not present in other nerves, and Thomson himself refers to the facts that neuro-fibromatosis has been discovered more than once on post-mortem examination when its existence was entirely unsuspected during life,

and that even an extensive neuro-fibromatosis may be unattended by any symptoms. How can anyone assert without a necropsy that a visible neuro-fibroma is the only change in the fibrous tissue of the same or other nerves?

Thomson knows of no authentic observation of the occurrence of degeneration of nerve fibres in any case of innocent solitary neuroma; he thinks, however, he has found degenerative changes in two cases of multiple neuro-fibromata. It is always difficult to decide this question, because the overgrowth of connective tissue separates the nerve fibres from one another, and in this way gives an incorrect idea of extensive destruction of nerve tissue. Making all due allowance for this fact, the reviewer believes that he also has observed degeneration of nerve fibres in multiple fibro-neuromata. Malignant tumors of nerves unquestionably cause destruction of nerve fibres.

Sarcomata of the sciatic nerve demand surgical treatment, and it is well to bear in mind some facts stated by Thomson. Recovery of function after the removal of the tumor has been usually remarkably good, but recurrence of the tumor has been the rule, and death from internal metastases has occurred in the majority of these cases. Thomson, therefore, concludes that although removal of the tumor alone has been successful in a very small proportion of cases of malignant neuroma, the best and usually the only chance lies in the early and high amputation; the rationale of this treatment being that we have to deal with a sarcoma which spreads upward along the interior of the affected nerve. Where amputation cannot be done division of the nerve above the tumor may relieve pain, or even division below the tumor may be desirable if the nerve cannot be cut higher. It is difficult to believe that much benefit can be obtained by cutting a nerve below the tumor. A rapidly growing neoplasm of a nerve will cause pain even though peripheral irritation has been cut off. Every physician knows of anæsthesia dolorosa. The sarcomatous degeneration of fibro-neuromata is peculiar in that it is not liable to cause visceral metastasis, but is liable to cause the sarcomatous change in neuro-fibromata of other parts of the body. We fear that Thomson's advice in regard to the treatment of new growths in nerves will not be invariably followed. The high amputation for the removal of a small malignant tumor of the sciatic might seem to some too heroic.

Thomson knows of no reliable facts in regard to the occurrence of sarcomata in the ganglionic enlargement of nerves. In reference to this we may mention that a few cases of endothelioma of the Gasserian ganglion have been described (Homén, Hagelstam, Dercum, Keen and Spiller.)

It seems curious that the fibromatosis of nerves does not extend to the membranes of the brain and spinal cord, as these are regarded as homologous with the sheaths of nerves, and yet involvement of the central nervous system in fibromatosis has never been observed. The central nervous system is, therefore, not considered in treatises on neuro-fibromatosis.

The treatment of neuro-fibromata showing no malignant change demands a few words in this review. Removal of one or more neuro-fibromata has been followed in some cases by greater activity and a generalization of the fibromatosis. The important question is, therefore, in regard to the treatment of these tumors. Thomson believes

that where the pain is agonizing it may be necessary to disregard the dangers attending removal, although it might be wiser to resect a portion of the nerve at a higher level or to amputate a limb. This advice requires careful consideration, because sarcoma seems to develop in neuro-fibromatosis in over 17 per cent. of the total cases recorded, and Thomson gives the detailed histories of two of his cases in which sarcomatous degeneration developed after removal of some of the neuro-fibromata. This form of degeneration seems to be exceptional in the plexiform tumors. The surgeon may well hesitate to cause paralysis by excising a portion of a nerve the seat of a few neuro-fibromata, and his hesitation may be much greater when he takes into consideration the question of amputation of a part or the whole of a limb. The patient in many instances will certainly object to an operation which appears to him unnecessarily severe, but sarcomatous degeneration in over 17 per cent. of cases of neuro-fibromatosis is not to be disregarded.

Bruns collected the records of forty-two cases of plexiform neuro-fibromata, but the number of reported cases as given by Thomson is sixty-two.

The illustrations used in this monograph are excellent. Most of them are from the author's own cases, but a few have been borrowed from other writers. The printing and binding are very good, except that in the copy before us several pages have been duplicated—a trifling fault, but one that causes annoyance until the cause of the confusion is recognized. W. G. S.

CONTRIBUTIONS FROM THE WILLIAM PEPPER LABORATORY OF CLINICAL MEDICINE. Published on the Phœbe A. Hearst Foundation. Philadelphia, 1900.

THIS is a noteworthy volume of 479 pages, representing thirteen distinct contributions to scientific medicine from the Pepper Laboratory of Clinical Medicine of the University of Pennsylvania. The volume, which is well edited and well illustrated, is issued in commemoration of the founder of the laboratory, the late William Pepper, an excellent likeness of whom fittingly forms the frontispiece. Surely the workers indebted to his wise provisions for the opportunity to pursue special studies could have selected no more appropriate method of testifying in a lasting form to their gratitude for his high generosity, "For, unlike any tribute wrought in stone or metal, it has the quality of increase. The results of the investigations here set forth will stimulate further investigations and lead to still greater increase of knowledge."[1]

The year 1900 is to be a distinguished year in American medicine, because it marks the inauguration on a large scale of the publication of memorial volumes, as shown by the appearance, simultaneously with the volume forming the subject of this notice, of the volume published by the pupils and friends of Prof. Welch in Baltimore in honor of the twenty-fifth year of his doctorate, and of the *International Contributions*

[1] From Dr. Councilman's address on the occasion of the presentation of the Welch "Festschrift."

to Medicine, in commemoration of Abraham Jacobi's seventieth birthday. Certainly, these three books, in contents, form, and objects, immediate and remote, compare favorably with publications of similar character in other countries. It is, we believe, a matter of congratulation that the time and opportunity are at hand for undertakings of this nature. The general effect can but be widely stimulating and helpful. The productiveness, originality, and resources of scientific medicine in this country are brought out well in all these volumes, and in no inferior degree in the volume under consideration, which represents the industry and achievements of but a single laboratory, and that of rather special scope. That the establishment of this laboratory has materially advanced the cause of scientific investigation in medicine in this country is shown clearly by the contributions in this volume, all of which present the results of original research.

The varied nature and general character of the contents of the volume are best indicated by giving the titles of the various articles:

Two Cases of Muscular Dystrophy, with Necropsy, by William G. Spiller, pp. 17–62 A Case of Amyotrophic Lateral Sclerosis in which Degeneration was Traced from the Cerebral Cortex to the Muscles, by William G. Spiller, pp. 63–106. A Contribution to the Study of (*a*) Iron Infiltration in the Ganglion Cells; (*b*) Forced Movements Due to Cellular Degeneration of the Cerebellum following Rattlesnake Poisoning, by D. J. McCarthy, pp. 107–119. A Fatal Case of Sulphonal Poisoning, by Alonzo Engelbert Taylor and Joseph Sailer, pp. 120–128. Melanotic Sarcoma of the Spinal Cord, by Joseph Sailer, pp. 129–147. Studies in Leukæmia, by Alonzo Engelbert Taylor, pp. 148–328. On the Pathology of the Erythrocyte, by Alfred Stengel, pp. 329–555. The Restitution of the Blood Plasma following Intravenous Saline Injection after Hemorrhage, by A. E. Taylor and C. H Frazier, pp. 356–367. The Influence of Immoderate Water-drinking upon Metabolism and Absorption, by D. L. Edsall, pp. 368–394. An Experimental Study of the Etiology of Appendicitis, by Charles H. Frazier, pp. 395–415. Primary Endothelioma of the Left Superior Pulmonary Vein, by Joseph Sailer, pp. 416–446. A Clinical Method for the Estimation of Breast-milk Proteids, by George Woodward, pp. 447–449. The Etiology of Pertussis; the Bacillus of Czaplewski-Henzel, by Joseph Walsh, pp. 450–474. Previous Contributions from the Laboratory, pp. 475–479.

Each article is a valuable and interesting contribution to the subject with which it deals. It is probably not invidious to mention the exhaustive reports of cases of muscular dystrophy and amyotrophic lateral sclerosis by the industrious Spiller; the extensive and deep study of leukæmia by Taylor, and the concise and able presentation of the pathology of the erythrocyte by Stengel. Sailer's cases of melanosarcoma of the spinal cord and of primary endothelioma of the left superior pulmonary vein are quite unique and of great interest. Frazier brings a valuable addition to an important but hitherto somewhat neglected phase of appendicitis, namely, the experimental study of its etiology. Walsh shows that the bacillus of Czaplewsky-Hensel, the organism that seems to be associated more closely with pertussis than any of the other numerous organisms reported in connection with this disease, probably belongs in the so-called pseudodiphtheria group; and the results of his injections with the serum of persons having had whoop-

ing-cough are certainly calculated to engage further attention. The more purely chemical and experimental physiological work of the laboratory is well represented by the articles of Woodward, Edsall, and Taylor and Frazier.

The list of previous contributions from the laboratory contains more than sixty articles by twelve different authors—a record that, taken in conjunction with the *Pepper Memorial Volume*, speaks of great activity since the inauguration of the laboratory, in 1895, "to encourage the prosecution of minute clinical studies and original researches, and to advance the interests of science by the publication of the results of such work." L. H.

PRECIS DE TOXICOLOGIE. CLINIQUE ET MEDICO-LEGALE. Par le DR. VIBERT. Paris: J. B. Bailliere et Fils, 1900.

SYNOPSIS OF TOXICOLOGY. CLINICAL AND MEDICAL LEGAL.

THE study of toxicology in the broadest sense has become one of great interest on account of the relations of the ordinary forms of intoxication with infections. The analogy of the conditions in the former and latter have led to certain valuable discoveries, and the methods of investigation pursued in the case of ordinary poisons have been carried out with bacterial intoxications with satisfactory results. The present work, however, is not an attempt at constructing any general scheme or of establishing a comprehensive system of toxicology; it deals rather with the classification of poisons, the discussion of their general action, and some consideration of special forms of intoxication. The author very wisely excludes all consideration of chemical methods, as these are of interest only to practical chemists. Considerable attention is given to the pathological lesions caused in experimental intoxication and the lesions discovered post-mortem in cases of poisoning. Regarding the classification, he advocates the eventual separation of groups representing certain definite forms of action. These groups may be separated according to the tissues which they especially attack and according to the kind of change that they induce. Experimental toxicology has already made it possible to establish some of these groups, as, for example, the poisons of the blood and the toxalbumins. The poisons of the nervous system, including cardiac poisons, would form another group; and still another would include such toxic substances as attack the cellular nutrition, like phosphorus. Unfortunately there are many poisons which cannot be placed in any one of the groups, because their action is insufficiently known, and because in other cases the intoxicant exercises different forms of action, and the relative importance of the different kinds of activity cannot as yet be properly estimated. A similar classification has been adopted by others. One which has seemed to us to be particularly useful divides the poisons into (1) corrosive; (2) parenchyma poisons; (3) blood poisons, and (4) nerve poisons. It is to be observed, however, that the poisons which are corrosive in certain strengths are parenchyma poisons when more slowly administered and in smaller dose, and some of the bodies which are blood poisons also produce changes in the fixed organs. It is unnecessary to

review at length the chapters dealing with the individual poisons. These are written with particular care for the needs of the clinician. The concluding chapters of the book, dealing with the toxalbumins, ricin, and abrin, the venom of serpents, the poisoning with mushrooms and tainted food, are all of particular interest.

Altogether the book is a useful synopsis for the practitioner, all the more as it details the treatment of the various forms of poisoning with particular care. A. S.

DISEASES OF THE NOSE AND THROAT. By J. PRICE-BROWN, M.D., L.R.C.P.E., Member of the College of Physicians and Surgeons of Ontario; Laryngologist to the Toronto Western Hospital; Laryngologist to the Protestant Orphans' Home; Fellow of the American Laryngological, Rhinological, and Otological Society; Member of the British Medical Association, Pan-American Medical Congress, the Canadian Medical Association, the Ontario Medical Association, etc. Illustrated with 159 engravings, including six full-page color plates and nine colored cuts in the text, many of them original. Pp. xvi., 470. Philadelphia: The F. A. Davis Co., 1900.

THE author, in apologizing for adding yet one more to the numerous text-books on the subject, states that his work is intended for the medical student and the practitioner who is obliged to do more or less nose and throat work in the daily routine of general practice. The book is well adapted for these purposes, although the author has, he says advisedly, left out altogether the consideration of some subjects which may be regarded as occupying the borderland between laryngology and general medicine, such as diphtheria and asthma, and about which, one can but feel, the average medical man might well need some advice from the specialist. It is also to be regretted that Dr. Price-Brown has seen fit to devote such a very small amount of space to the anatomy and physiology of the nose and throat. It is true these matters can be looked up in text-books on anatomy, but in these books they are not given in such a way as to bear on some of the practical points which can be emphasized only by considering them in their clinical bearing. His discussion of the pathology and symptomatology of the morbid conditions met with in the nose and throat is sufficient for practical purposes, though concise in many particulars. The sections devoted to the treatment of morbid conditions of the upper air-passages are uniformly good. The author writes in a terse but very attractive way, and in describing methods of treatment he has chosen those which can be most readily carried out by the practitioner. In describing operative measures he occasionally has made his descriptions somewhat too brief to be altogether lucid, but it is unlikely that any save the specialist would undertake the operations to which this criticism applies. An innovation is the use of the metric system in the various prescriptions given throughout the book. Fortunately, however, for the average reader a translation of the prescription into the ordinary system is given at the foot of the page, so that he can understand it.

The illustrations are—many of them—taken from standard works, such as Lennox Browne and Bosworth, but they are interspersed with

a considerable number of original ones of real merit, particularly some colored plates of frozen sections. The typography of the book is all that could be desired. F. R. P.

THE YEAR-BOOK OF THE NOSE, THROAT AND EAR. The Nose and Throat, edited by G. P. HEAD. The Ear, edited by ALBERT H. ANDREWS Pp. 274. Chicago, Illinois: Chicago Medical Book Co., 1900.

WORKS of this kind are of the greatest value, particularly since the *Index Medicus* is no longer published. The editors have given abstracts of most of the leading articles on laryngology and otology which have appeared, both in this country and Europe, during the year. The abstracts are judiciously made, sufficient of the original article being retained to illustrate its trend. The work does not pretend to be a complete list of all of the literature of the subject, but is very good so far as it goes. It is to be hoped the editors will feel sufficiently encouraged to continue their labors, as they will surely meet with the due appreciation of the members of the profession who are interested in the specialties with which they deal. The book is a handy volume, clearly printed, and reflecting credit on the publishers. F. R. P.

BACTERIA: ESPECIALLY AS THEY ARE RELATED TO THE ECONOMY OF NATURE, TO INDUSTRIAL PROCESSES AND TO THE PUBLIC HEALTH. By GEORGE NEWMAN, M.D., F.R.S. (Edin.), D.P.H. (Camb.), etc., Demonstrator of Bacteriology in King's College, London. The Science Series. New York: G. P. Putnam's Sons. London: John Murray, 1899.

THE scope of the work is indicated in the title and in the following extract from the preface: "The present volume is not a record of original work, nor is it a text-book for the laboratory. . . . It is an attempt, in response to the editor of the series, to set forth a popular scientific statement of our present knowledge of bacteria." Books of this character serve a useful purpose, and the one before us contains a store of valuable knowledge which is presented in an attractive manner. Our constant dependence on the functional activity of germs in many of the ordinary pursuits of life has been well brought out, and the author is to be especially commended for the picture he has given of microbes as the friends and allies of mankind rather than as their enemies. The part played by them in the purification of sewage, and the removal of dead organic matter by its conversion into forms easily assimilated by plants as food, through the process of "nitrification" is well described, while the account of sewage treatment by the "septic tank and cultivation beds," which has been in use in England for several years, is particularly interesting.

The chapter on Milk, Milk Products, and Other Foods gives a comprehensive review of modern dairy methods, including the use of pure culture "starters." The author speaks with approval of the addition

of preservatives, such as boric acid, salicylic acid, and formaldehyde, to milk, a practice entirely discountenanced by physicians in America. It has been abundantly demonstrated that with reasonable care milk can be drawn clean and preserved by cold alone for considerable periods of time.

The chapter on Disinfection contains no mention of "milk of lime," which is justly regarded as one of the cheapest, safest, most efficient and easily obtained disinfectants known, and especially valuable for household use.

While the book contains much that the physician can read with profit, it is more suitable for the general reader, for whom it is evidently intended.

The book is marred by numerous errors, the nature of which indicates that the proof was read by someone other than the writer, and who had no technical knowledge of the subject, and also in several places by a looseness of expression and confusion of terms, for which the author must be held accountable. Such errors are particularly objectionable in a work of this nature, designed to be read by those having no special knowledge of the science and who are, therefore, unable to detect the mistakes. Many of the illustrations are unusually good, notably the micro-photographs, but several of the cuts are inexcusably poor, detracting from both the appearance as well as the value of the book. The binding and printing are excellent. M. P. R.

GYNECOLOGY: A MANUAL FOR STUDENTS AND PRACTITIONERS. By MONTGOMERY A. CROCKETT, M.D., Adjunct Professor of Obstetrics and Clinical Gynecology, Medical Department University of Buffalo; Attending Gynecologist to the Buffalo General and Erie County Hospitals. Edited by B. B. GALLAUDET, M.D., Demonstrator of Anatomy and Instructor in Surgery, College of Physicians and Surgeons, Columbia University, New York; Visiting Surgeon, Bellevue Hospital. New York and Philadelphia: Lea Brothers & Co., 1900.

THE book has so many good points that it is a pity that the author did not restrict himself somewhat more closely in his range of subjects. No book of 351 pages can do justice to Gynecology in its entirety if anything more comprehensive than a syllabus is attempted.

It would have been much better if all technique of major operative procedures had been omitted, and in the space thus gained a more detailed account of operations possible to the general practitioner had been substituted.

Certain statements strike one as entirely too dogmatic, as for instance the absolute interdiction of the use of silk ligatures within the abdominal cavity, while the use of the stem pessary is at least not a form of treatment to be recommended without a more detailed warning of its danger.

The book will well repay one for the time spent in its reading, however, the main fault with it being that the author has attempted to include too much material in the space at his command.

W. R. N.

PROGRESS

OF

MEDICAL SCIENCE.

MEDICINE.

UNDER THE CHARGE OF

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On the Cultivation of Typhoid Bacilli from Rose-spots.—RICHARDSON (*The Philadelphia Medical Journal*, March 3, 1900, p. 514) points out the scientific and diagnostic value of the rose-spots in typhoid fever as determined by recent research. That the rose-spots are due to a metastasis of the typhoid bacilli from the intestine to the skin has been frequently demonstrated since the discovery of the typhoid bacillus by Eberth. In investigating this point, however, many negative results had been obtained.

Neufeld has recently reviewed the subject and gives some remarkable results obtained by himself. He found that the efforts to cultivate the typhoid bacillus from the rose-spots had hitherto been so often negative that they had little value either from a scientific or from a diagnostic stand-point. Neufeld's results, however, have been extraordinary in that he cultivated the typhoid bacillus in thirteen out of fourteen cases. He attributes his good results to the fact that he as quickly as possible transferred the drop of blood from the rose-spot to a tube of nutrient bouillon. In this way he was able to dilute the bactericidal substances of the blood so thoroughly and quickly that they no longer destroyed the typhoid bacilli, as they do when cultures are taken in the ordinary way. To the lack of observance of this method of technique Neufeld attributed the frequent negative results of previous workers.

Neufeld compared the date of the earliest appearance of the Widal reaction with the earliest day of the disease on which he had obtained the typhoid bacillus from the rose-spots. This was done in eight cases, and he found that in seven out of the eight cases the diagnosis made from the rose-spots was, on an average, six days ahead of that made by the Widal test, whereas in only one case was the Widal reaction obtained first.

Curschmann, stimulated by Neufeld's work, undertook a similar investigation, also, with remarkable results. He found the typhoid bacillus in fourteen out of twenty cases examined bacteriologically.

Richardson made a bacteriological examination of the rose-spots in six cases, using the same technique as Neufeld, with the exception that the rose-spot was frozen with a spray of methyl chloride before it was incised. He obtained the typhoid bacillus in five of the six cases. In all the cases the positive result of the cultures from the spots antedated the Widal test by an average of six days. His work confirms a further point ascertained by Neufeld, namely, that not every spot can be depended on to yield bacilli. Five or six spots should be incised in every case.

Concentration of the Urine and Blood in Kidney Diseases, and the Cause of Uræmia.—LINDEMANN (*Deutsches Archive für klinische Medicin*, Band 65, p. 1) has an article on this subject giving the results of a large number of examinations in various diseases. As a result of these examinations he came to the following conclusions:

1. The concentration of urine can be determined with great accuracy by means of the freezing-point method. This method is superior to others for determining the concentration, such as specific gravity and the dry residue, as it does not depend on the weight of the single constituents, but only on their molecular number. Such a determination permits a conclusion as to the functional capacity of the kidneys.

2. The determination of the lowering of the freezing-point of urine, along with the measurement of the daily excretion, allows one to distinguish between albuminuria independent of inflammation in the kidney from that caused by nephritis.

3. The freezing-point of normal urine—moderate quantities being passed—varies between —1.30 and —2.30, and variations as great as —0.90 and —2.73 are very unusual.

4. The lowering of the freezing-point in all inflammations of the kidney, and along with that the concentration, is much less; with moderate daily quantities the freezing-point is usually less than —1.

5. The lowering of the freezing-point shows characteristic differences between parenchymatous and interstitial nephritides; in the former the lessened concentration is more marked, and is especially so with small quantities of urine.

6. The lessened concentration is often such that the urine shows a lower freezing-point than normal blood-serum.

7. The determination of the concentration of urine does not permit one to distinguish between an acute and chronic parenchymatous nephritis, but it enables one to recognize oncoming recovery by the approach of the freezing-point to normal.

8. The lowering of the freezing-point allows one often to recognize the transition of chronic parenchymatous nephritis into secondary contracted kidney; it then increases and reaches values similar to those in primary contracted kidney.

9. Other albuminurias, such as those in congested kidney, in fever, in cystitis, and pyelitis are characterized by the absence of a lessening of the reduc-

tion of the freezing-point. Exception must be made in cases of collapse, in which small quantities of urine are passed with lowering of concentration.

10. In cystitis and pyelitis a lessening of the concentration with moderate quantities of urine indicates the extension of the inflammation into the renal tissues with great probability.

11. The estimation of the total quantity of the substances excreted with the urine in nephritis frequently permits a conclusion as to retention of other substances that should be excreted.

The author has also applied his observations to the theory of uræmia, and with reference to this makes the following conclusions:

1. In nephritis the concentration of the blood-serum is normal as long as there are no uræmic symptoms.

2. When uræmia occurs there is a concentration of the blood-serum, and its osmotic pressure is increased. The lessening of the freezing-point sometimes amounts to as much as —0.70.

3. This elevation of osmotic pressure is the general expression of the existing abnormality in the uræmia, and most of the changes found in uræmia can be sufficiently explained by it.

4. The phenomena which appear after injections of large quantities of concentrated salt solution in the circulation are the same as those that occur in uræmia; they appear with the increased concentration of the blood when the elimination of accumulated substances from the blood can no longer go on because the absorptive power of the tissues and organs is exhausted.

Venous Thrombosis as a Complication of Cardiac Disease.—WELCH (*Festschrift in Honor of Abraham Jacobi*, p. 461) reports four cases of thrombosis of the peripheral veins complicating cardiac disease, and gives abstracts of twenty-three other cases which he has been able to collect from the literature. Only cases with thrombosis of the peripheral veins are included.

Dr. Welch summarizes the four cases as follows:

CASE I.—Aortic and mitral insufficiency. Adherent pericardium; broken compensation; thrombosis of the left innominate, jugular, subclavian, and axillary veins. Death.

CASE II.—Mitral stenosis. Thrombosis of the left jugular, axillary, subclavian, and innominate veins; embolism of the left popliteal artery. Recovery from effects of vascular occlusion.

CASE III.—Mitral and aortic insufficiency. General anasarca; thrombosis of the left axillary and brachial veins. Death.

CASE IV.—Mitral insufficiency. Thrombosis of the left femoral vein. Recovery from the effects of the thrombosis.

These four cases, with the twenty-three collected from the literature, make a total of twenty-seven cases of thrombosis of the peripheral veins complicating cardiac disease.

The most remarkable feature of the series is the location of the thrombi. Twenty-three were thromboses of veins supplying the upper extremities or the neck, or both, mostly of the left side, and only four were thromboses of veins supplying the lower extremities. This ratio is remarkable when one considers that Bouchut's statistics show that the ratio of venous thrombosis of the upper extremity is to those of the lower as one is to fifty. The four

instances of venous thrombosis of the lower extremities had little in common with the remaining twenty-three. Two were in old persons with some arterial atheroma. The thrombosis was on the left side in three and bilateral in one, thus conforming to the general rule. The remaining twenty-three cases of venous thromboses of the neck and arms in cardiac disease constitute a separate and distinct group characterized by features of special interest.

Seventeen cases were in females, four in males, and of two the sex was not stated. These figures show that this form of thrombosis is especially frequent in females. Attention in this connection is drawn to the fact that mitral stenosis is particularly common in women between the ages in which these cases occurred.

Of the 17 patients with thromboses of the neck and arms whose ages were stated one-half, or 8, were between fifteen and thirty years of age. The youngest was nine and the oldest fifty-two.

In 2 cases the valvular lesion was not stated. Of the remaining 21 cases there was organic disease of the mitral valve in 20; in the other case there was aortic insufficiency, with relative mitral incompetence. Of the mitral lesions, mitral stenosis, with or without insufficiency, took the lead.

The valvular lesion was caused by rheumatism in a little over one-half of the cases. In a great majority of the cases the thrombosis appeared during a condition of broken compensation.

As to the location of the thrombi, the striking feature is that in 21 out of the 23 cases the veins of the left side were involved; of these 14 were unilateral and 7 bilateral. In only 2 cases were the veins of the right side alone affected. The commonest starting-point for the thrombus was the lowest part of the left internal jugular, or of the left internal jugular vein and the left innominate or subclavian vein near the entrance of the jugulars.

The thrombi were mixed, the prevailing color being dark red. In a few instances the thrombus was centrally softened. Bacteria were searched for in only three cases and were found only in Welch's first case, the organism being the streptococcus pyogenes.

The local symptoms were those usually associated with venous thrombosis —pain, tenderness, œdema, the presence of hard, sensitive venous cords, and distention of the superficial veins.

The prognosis in these cases is grave. Of the 23 cases 19 ended fatally and 4 recovered. The gravity of the prognosis apparently results mainly from the circumstance that the occurrence of the thrombosis is in itself an index of extreme failure of compensation of the valvular lesion, being sometimes scarcely more than a terminal event.

Although five of the cases were reported as instances of rheumatic phlebitis, Welch doubts whether rheumatism was the correct explanation given in these cases. In the whole series he thinks that rheumatism had only a minor share in the immediate causation of the thrombosis. French writers, particularly Peter, Parmentier, Kahn, and Huchard, hold that the underlying cause is some alteration in the chemical composition of the blood similar to the changes in the blood which are held to cause the thromboses in tuberculosis and cancer.

The explanation of the greater frequency of thrombosis of the veins of

the left upper extremity is based by most observers on anatomical lines. The return of the venous blood from the left upper extremity is more difficult than the right, owing to the greater length and obliquity of the left innominate vein. Welch suggests also the effect of pressure, either direct or indirect, on the left subclavian vein from the dilated left auricle and dilated large pulmonary vessels.

The frequency with which the thrombus starts from the lower ends of the jugulars is explained by von Recklinghausen as being due to the whirling or eddying movement (*Wirbelbewegung*) of the blood at this point. This whirling movement is due to local anatomical causes. Welch strongly supports the theory.

The writer lays great stress on the view that the thrombi are bacterial in origin. This view is supported by the results of bacteriological examinations made of thrombi in the author's laboratory. Of forty-four thrombi examined the cultures showed micro-organisms in thirty-four. Welch thinks that the bacterial theory of causation is the most satisfactory for the present.

An Analysis of Sandy Matter (Sable Intestinal) from the Human Intestine, with Special Reference to a Contained Pigment of Unusual Character.—THOMSON and FERGUSON (*The Journal of Pathology and Bacteriology*, February, 1900, vol. vi. p. 334) give the results of their analyses of the so-called intestinal sand passed in the stools of a female patient, aged thirty years. The patient had for years suffered at intervals from symptoms of catarrh and dilatation of the stomach, associated at times with signs of decided neurosis. Just after one of the attacks it was noticed that the movements contained sandy matter. The diet during this time was limited to milk and lime-water. Three samples of sandy matter were obtained. The first of the samples obtained weighed about half an ounce; the second and third about six drachms each.

Collected at the bottom of a vessel the sediment presented a somewhat brownish-yellow appearance strongly suggestive of uric acid, and even when examined microscopically in the moist state the resemblance to uric acid was very striking. An application of the murexide test gave negative results, and no gas was evolved when the sand was treated with sodic hypobromite. The sand was evidently not of vegetable origin, as there was no trace of sclerenchymatous tissue in any of the samples examined microscopically.

A chemical analysis of the sand showed it to contain 71.5 per cent. of inorganic and 28.5 per cent. of organic matter. A further analysis of the inorganic matter gave 11.5 per cent. calcic carbonate, 87.3 per cent. of tricalcic phosphate, and 1 per cent. of insoluble residue (silica.)

Thomson and Ferguson made some careful studies of the nature of the pigment contained in the sand. As a result of their studies they were led to conclude that the pigment was not one of those usually described as derived from the normal pigments of the bile. Its insolubility in chloroform, ethylic alcohol, and ether excluded bilirubin, bileverdin, bilifuchin, bilifirasin, stercobilin, and cholehæmatin; while its solubility in dilute acids excluded bilfhumin (Stadeler).

They further concluded that the intestinal sand, from its ready solubility

in dilute acids, was formed neither in the upper part of the small intestine, where practically unchanged bile-pigments are present, nor in any part of the colon, in which stercobilin is the prevailing pigment, but in the ileum, where the intestinal contents are most likely to be alkaline in reaction. They think that the contained pigment is most probably a substance intermediate between the ordinary bile-pigments and their ultimate product—stercobilin.

A Case of Typhoid Infection without Intestinal Lesions, with Positive Widal Reaction.—Ophüls (*New York Medical Journal*, May 12, 1900, p. 728) adds another instance to the gradually increasing number of cases that have been reported of typhoid fever without intestinal lesions.

The patient, a man, twenty four-years of age, came under observation on September 4, 1899. He was unconscious, and no definite history could be obtained. The urine gave the diazo reaction. The Widal test was positive, with a dilution of 1 to 40. There was marked abdominal tympany. The left lung gave impaired resonance throughout, and there were râles over both bases. The patient's temperature ranged between 100° and 106° F. He was treated by calomel, stimulants, and cold baths. Death occurred on September 11th.

An autopsy was obtained and the following anatomical diagnosis was made: Typhoid infection without intestinal lesions; necrotizing bronchopneumonia, with recent pleuritis. Inflammatory softening of the spleen, enlargement and multiple necroses in the lymph-glands at the base of the mesentery; cloudy swelling of the kidneys and pancreas; multiple necroses in the liver; acute inflammation of the appendix; multiple hemorrhages on mucous membrane, the bladder, and renal pelves; cyanosis; œdema under the eyes.

Cultures from the spleen gave the typhoid bacillus, which was agglutinated by the serum from a case of typhoid fever with a dilution of 1 to 40. The colon bacillus was obtained from the spleen, as well as from the kidneys, liver, and lungs.

According to Ophüls, the view that typhoid fever could occur without intestinal lesions was held even before the Eberth-Gaffky bacillus had been discovered—that is, before it was possible to identify these cases positively as typhoid fever. Andral seems to have been the first to call attention to this fact. Similar observations were recorded by Brunschwig, Litten, Moore, Church, Coupland, and Goodall. Most authors agree that the first really convincing observation supported by bacteriological proof was made by du Cazal in 1893. Ophüls claims that of all the cases reported as typhoid infection without intestinal lesions there are only five—that of Flexner and Harris, the three of Lartigau, and his own—in which the differential characteristics between the typhoid bacillus and allied forms have been sufficiently carefully followed out to allow of a definite statement that these cases were actually typhoid infection.

The writer discusses the probable mode of entrance into the system of the typhoid bacilli in these cases. Several of those who have reported such cases hold that the respiratory tract or the bile-ducts or gall-bladder have been the seat of entrance. While admitting this possibility, Ophüls seems to be strongly of the opinion that notwithstanding the absence of gross intestinal lesions

at autopsy, the intestinal mucosa has probably been the point of entrance of the organism into the system. He thinks that the enlargement of the mesenteric lymph-glands found in several of the reported cases, including his own, is very suggestive in this regard. He seems inclined to the view that in typhoid fever the intestinal lymphatic tissue may undergo hyperplasia and resolution without ulceration, and believes that in some of the cases reported as typhoid fever without intestinal lesions such hyperplasia had at one time existed and that there had been ample time for a *restitutio ad integrum* before the post-mortem took place.

On the Etiology of Head-shaking with Nystagmus (Spasmus Nutans) in Infants.—THOMSON (*Festschrift in Honor of Abraham Jacobi*, 1900, p. 65) contributes an interesting paper on a functional co-ordination neurosis which affects young children, and which he chooses to designate under the names spasmus nutans or head-shaking.

Clinically there are two cardinal symptoms—involuntary head movements and ocular nystagmus. These are both present in the majority of cases. In some, however, only head-shaking is observed. The association between the head movements and those of the eyes is illustrated by two facts. When closure of the unsteady eyes takes place naturally in sleep, or is artificially produced by the application of wadding and a bandage, the head-shaking ceases; also when the head is passively steadied by the hands the nystagmus increases or may appear for the first time.

Thomson's paper is based on the study of eighty-eight cases collected from the literature, and particularly on thirty-five other cases which came under his own personal observation.

Concerning the etiology of the disease, the nervous mechanism, whose function is at fault, is evidently that which includes the semicircular canals in its circuit, and which regulates the co-ordination of the movements of the eyes with those of the head. Alex. Bruce thinks that the nucleus of Deiters is in all probability the seat of the disturbance.

Over three-fourths of the published cases, including Thomson's own, began between four and twelve months of age. This corresponds to the period during which the child is slowly learning to co-ordinate the movements of the eyes with those of the head. The condition is commoner in females, twenty of Thomson's thirty-five cases being in girl infants. Rarely is there any neurotic history in the family, and the intellect of the child is not impaired. Reflex irritation is a minor causative factor.

Defective light in the home seems to be the most important, if not essential, element in the causation. An investigation showed that practically all the cases occurred in insufficiently lighted houses. In further support of the defective light theory are the facts that in the majority of the cases the symptoms began in December or January, the darkest months in the year, and that the disease is practically confined to towns.

The vast majority of the infants suffer from rickets. In thirty-three of Thomson's thirty-five cases there were undoubted signs of the disease. Doubt is expressed whether the connection between rickets and spasmus nutans is of exactly the same kind as that between rickets and laryngismus, convulsions and tetany.

Thomson says: "From a review of these etiological factors we may conclude that the age of the patients, the absence of sufficient light in their surroundings, and the presence of rickets are the most important influences in determining the onset of the disease; likewise that anything which temporarily or permanently lowers the vitality may predispose to its occurrence."

SURGERY.

UNDER THE CHARGE OF

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A Contribution to the Surgery of Perforated Gastric Ulcer.—MITCHELL (*British Medical Journal*, March 10, 1900) has collected thirteen cases of gastric ulcer that have recently been operated upon. The statistical value is due to the fact that successful and unsuccessful cases are alike recorded, and the result—thirteen cases, with six recoveries—must be regarded as eminently satisfactory. The first case operated on by the author was nearly hopeless, as it was sixty hours after perforation. In another the wall of the stomach was so rotten that it tore to the extent of one and one-half inches, and a large mass of tissue, apparently malignant, occupied the anterior wall of the organ at some distance from the ulcer.

The symptoms of the average case are given as follows: A patient, male or female, with or without a history of previous gastric symptoms, is suddenly seized with violent abdominal pain, immediately followed by profound shock and collapse, and perhaps by vomiting. The pain, which may at first have been localized, rapidly becomes general. The abdomen becomes intensely tender, with its muscles hard and rigid. On percussion there is a tympanitic note all over; possibly there is a diminished area of hepatic dulness, especially in front. The bowels are inactive. The patient is cold and livid, with subnormal temperature, has a quick, feeble pulse, thoracic respiration, anxious expression, and suffers from intense thirst. Soon a period of repose commences, when the sufferer feels distinctly easier, the pulse improves a little as the initial shock passes off; the abdominal retraction is replaced by slight distention, and liver dulness becomes markedly diminished. In a short time, however, the pain returns, tenderness increases, the temperature rises, and the patient exhibits all the signs of general septic peritonitis; or in the more fortunate cases the peritonitis is localized by adhesions, and an abscess forms. Thus the characteristic symptoms of per-

foration are sudden onset, violent pain, profound shock, intense tenderness, rigidly contracted abdominal muscles, shallow thoracic respiration, and absence of liver dulness.

These cases, without the interference of the surgeon, are practically hopeless, with a death-rate of over 95 per cent. The chief factors in successful intervention are, first, early diagnosis and early operation. Once you have suspected that your patient suffers from the symptoms of perforation, there is not a moment to be lost. To wait for the primary shock to pass off is unnecessary, because sufficient time must elapse in preparing for so grave an operation. The importance of early operation is demonstrated by a table that shows 77 per cent. of recoveries in cases operated on up to twelve hours; 33 per cent. in cases operated on between the twelfth and twenty-fourth hours, and 29.4 per cent. when operated on after twenty-four hours. It cannot be too clearly understood, therefore, that the lives of these patients depend on the promptness and energy of the physician who first sees the case, even more than on the skill of the operating surgeon. Above all things, the use of morphine should be avoided, if possible, until a final diagnosis is made and the line of treatment decided upon.

The other points of importance to be noted previous to operation are: (1) The nature of the last meal taken; (2) the interval between the last meal and the occurrence of perforation; (3) the position of the patient at the time of perforation. These factors are valuable in determining the distance to which the food has been driven, and the direction. In point of time the perforation usually occurs about two hours after a meal. The longer this interval the more complete will be the process of digestion and the smaller the quantity of food remaining in the stomach. The danger due to extravasation will be proportionately diminished.

From his observations in eleven of the reported cases which he operated upon or at which he was present, the author derives the following lessons: 1. The incision in the first instance should be a fairly small one, and the peritoneal opening as small as possible, in order that the gas may escape slowly. Once all doubt as to the diagnosis has been set at rest, the wound may be rapidly enlarged to the required length by the scissors. 2. The best guide to the ulcer seems to be the presence of adhesions. Having drawn gently on the stomach, you find that in some directions it is more fixed than in others. On running the finger down to this area you will generally come on a zone of induration, in the midst of which the ulcer is almost certain to be found when the adhesions have been separated. Of course, cases occur in which perforation takes place so rapidly after the onset of the ulcer that there is no time for adhesions or for induration, but they are very rare.

The bubbling up of fluid and other gastric contents is not necessarily a guide to the seat of perforation. Should a careful search fail to show the ulcer on the anterior surface it will be necessary to open the lesser sac of peritoneum, and this can be most easily done by tearing through the layers of the great omentum, when the posterior surface can be examined. In at least two cases he found it necessary to divide the left rectus transversely, in order thoroughly to expose the ulcer. It is not always possible to bring the stomach and perforation into the abdominal wound; in fact, it is usually impossible.

The ulcer need not be resected; serious hemorrhage is likely to follow. A running suture closes the wound and is buried by Lembert sutures.

The peritoneal cavity may be cleansed: 1. By sponging with sterile gauze pads, which are wonderfully effectual in removing coarse material and rapidly soaking up fluid. 2. By thorough douching with boiled water or normal salt solution. Of the six successful cases four were sponged alone; one was douched alone; while in one, in which the gastric contents had reached the pelvis, both methods were employed. The douche was employed in three unsuccessful cases, but they were at the same time the most unfavorable of the five. The resisting power of the peritoneum is the greatest feature.

Drainage should never be omitted. A gauze drain is gradually taking the place of the older methods, and a strand of this material should be introduced so as to lead down the line of suture, and one into each subphrenic space, as it is here that the abscess most frequently occurs. Although often difficult to remove on the third or fourth day, it will come away easily at the end of a week.

Perforating Duodenal Ulcers—WEIR (*Medical Record*, May 5, 1900) says of this affection that it is much more rare than the ulcer of the stomach; is much more difficult to diagnosticate properly, and is more apt to be confounded with other more distant surgical lesions, such as appendicitis, etc.

The following contrasting symptoms have been grouped as an aid to this differential diagnosis:

Gastric ulcer: (1) More frequent in women; twenty-fifth to fiftieth year. (2) Pain promptly after eating. (3) Pains relieved by vomiting. (4) Frequent biliary, mucous, and food vomiting. (5) Marked dyspeptic symptoms. (6) Frequent bloody vomiting. (7) More seldom bloody stools.

Duodenal ulcer: (1) Occurs more frequently in males. (2) Pain in right hypochondrium or to the right of the parasternal line. (3) Comes on one or two hours after meals. (4) No relief by vomiting; latter not frequent. (5) Bloody stools (melæna or bright blood) more common than bloody vomiting. (6) Jaundice, if present, would contribute to the diagnosis.

The usual symptoms of perforation are the following: Great pain is usually felt at the epigastrium or to the right of this region, as was noted twenty-six times in the author's forty-seven cases. It has a few times been observed at the umbilicus and in the left side; but in twenty-three others of the forty-seven instances it was simply recorded as abdominal pain. Vomiting often follows the attack of pain. It occurred in twenty-eight out of the thirty-four instances. Shock is not often met with, but may be severe and fatal. Peritoneal symptoms rapidly develop, with a tendency in some cases to be localized in the upper part of the abdominal cavity and in the right side; when these signs show themselves mostly to the right and at or below the level of the umbilicus, an appendicitis is necessarily simulated. When the liver dulness has disappeared nearly up to the mammary line, air extravasation may be suspected, and when present it will aid in establishing a diagnosis. This symptom of loss of liver resonance, unless marked, is so often found to be due to a distended colon that it should not be much relied on.

In considering the diagnosis of perforated duodenal ulcer as just given the author feels that more weight and attention should be given, first, to the

previous history, which shows, contrary to the opinions of many anterior observers, that in the fifty-one collected cases of operation for the relief of such conditions there was a history of gastric or dyspeptic symptoms given in twenty-five out of the thirty-four instances in which this point was noted; secondly, the fact that the initial or early pain was developed in twenty-six instances out of forty-seven in the epigastrium is also important; and in the right hypochondrium thirteen times. The third factor of value in the diagnosis as well as the treatment of the symptoms of perforation peritonitis, whether from stomach, duodenum, gall-bladder, appendix, or any other part of the intestinal tract, is the prompt resort to an exploratory incision. This need of an early determination of the site of the perforation has been shown frequently. The mortality in these cases clearly depended on whether the patient underwent surgical intervention within twenty-four hours from the inception of the perforation.

The results in the fifty-one cases reported bear out this conclusion. There were twenty-five cases in which the lesion was recognized and closed at the time of operation; of these thirteen underwent operation after thirty hours' delay, and all resulted fatally; twelve other patients were operated on within that time, and eight survived, giving thus only 33⅓ per cent. of mortality. The mortality was formerly 60 per cent. Thus there has been great improvement in the past five years. Before that time in 70 per cent. of the cases operated on for duodenal ulcer it was not found; it was found and sutured in 25 per cent. In only two cases, or 10 per cent., was the possibility of a duodenal perforation considered. Contrast this with the thirty-one cases operated on since 1895, when the analogous surgery of gastric ulcer began to develop. Of these thirty-one cases the perforation was not found in only 11 per cent. It was found and sutured in twenty-six cases, or 65 per cent. Its presence was considered in diagnosis in eleven cases, or 35 per cent.

The Employment of Local Anæsthesia in the Radical Cure of Certain Cases of Hernia, with a Note upon the Nervous Anatomy of the Region. —CUSHING (*Annals of Surgery*, January, 1900) bases his paper upon forty-nine cases in which the radical cure has been performed under regionary anæsthesia.

Almost all cases of hernia, with the possible exception of those in young children, could undoubtedly be subjected to the radical operation under similar local methods; but when general anæsthesia can safely be administered, for various reasons it is much to be preferred by both patient and operator.

The factors that have determined the employment of the local anæsthetic in these cases have been advanced age, chronic bronchitis and emphysema, tuberculosis, laryngeal or pulmonary, cardiovascular changes of marked degree, chronic nephritis, and, above all, the shock and vomiting in strangulation.

The two conditions chiefly responsible were the combination of arteriosclerosis with cough from chronic bronchitis and emphysema in patients past middle life, and the shock and vomiting associated with strangulation.

He discusses in detail the reasons for operating with the reason for avoiding the anæsthetic. The operation was indicated either on account of the annoyance of the hernia, though operation was not absolutely necessary, or

on account of strangulation, in which there is urgent demand for operation. The femoral operation and that in women offers so little difficulty under a local anæsthetic that it is unnecessary to discuss it in detail.

Among the cases reported are fourteen patients over sixty years of age who have been operated upon not for emergency reasons, but from choice.

"For cases of strangulation local anæsthesia is especially adapted. It is difficult or impossible to foretell the condition of the imprisoned bowel, and though the results in the viable cases are always successful, provided the patient escapes post-anæsthetization sequelæ (unfortunately, not an infrequent complication), the mortality of those cases in which the gut is found to have lost its viability has always been high. It is in the experience of many to have seen such cases die under a general anæsthetic on the operating-table. The extreme degree of toxicity of the contents of the proximal bowel, especially when the strangulation is low, is such that patients apparently in good condition may succumb to an auto-infection even after relief of the strangulation." "It is in such cases as these that general narcosis—even leaving aside the dangers of inhalation pneumonia, since constant vomiting is usually an accompaniment of these conditions—should be avoided, as it is often the additional burden which prevents recovery. This is as true of the cases in which the bowel is viable as of those with a gangrenous loop. The patient's apparent state often belies the condition of the constricted bowel. It is not uncommon to have an individual walk into the hospital with a strangulated gut which has lost its viability. On the other hand, an imprisoned but viable loop may have caused intense shock and prostration. It is for such reasons that exploration under regionary anæsthesia is demanded.

"Under a local anæsthetic without danger to the patient the sac may be exposed, the constriction relieved, the gut, if viable, reduced, and, depending entirely upon the patient's condition, a radical cure may be completed at the same time or at a later date, when general narcosis, if desirable, may be employed. If the gut is not viable, experience has demonstrated that the immediate establishment of an intestinal fistula is much the safest procedure, as this permits the immediate escape of the retained toxic products from the proximal bowel. This is readily accomplished under the local anæsthetic, and at a later date, when the patient has fully recovered, the intestinal suture may be performed with much less risk."

This series of operations has given the author the opportunity to study out with great care the distribution of the cutaneous nerve supply. The observations made are of great anatomical and physiological value, while the exact knowledge of the distribution throughout this area is essential in operating by this method.

In performing these operations the author has found Schleich's No. 2 mixture, containing 1 to 1000 parts of cocaine and 2 to 1000 parts of salt, very efficient and more reliable and lasting in its effects than the eucaine-β solutions. While, contrary to the experience of many, he has found that one or two sterilizations fail to diminish its efficiency. For anæsthetization of the individual nerve trunks he has used a 0.5 to 1 per cent. sterilized solution of eucaine-β or cocaine, which is injected directly into the nerve.

In performing the operation the patient is placed in bed for a day or two to accustom him to the position and to evacuate the bowels and bladder

while supine. Three-quarters of an hour before operation a tenth or an eighth of a grain of morphine is given, and another such dose at the time of operation. The skin is infiltrated with the Schleich solution and incised. All bleeding is stopped, as a dry wound is essential to the dissection. It is unnecessary and useless to attempt to anæsthetize the panniculus. It is not fitted for infiltration, and at the upper angle practically no nerves are encountered. This can be avoided by carrying the incision downward only at the upper angle to the aponeurosis, which is then opened in the line of the fibres from the external ring, and the iliohypogastric and inguinal nerves immediately cocainized with a 1 per cent. solution as they lie under it. After this procedure the lower angle of the incision may be painlessly carried down to the external ring and the remaining intercolumnar fibres of the aponeurotic insertion divided. The combined ilio-inguinal and genital branch, which has been cocainized at the outer limit of its exposure, is now reflected to one side or the other, care being taken not to divide it, since this leads apparently to more or less permanent paralysis of the cremaster, which is to be avoided. The rest of the operation can be completed without pain. The subcuticular silver-wire suture used in closing the skin can be placed in the infiltrated skin area without pain.

The advantages of the local anæsthetic: There is an avoidance of unpleasant or dangerous post-etherization sequelæ. There is no vomiting or retching to put strain on the sutures. Urinary disturbances are much less apt to occur, and catheterization is rarely necessary. The diet continues as before the operation. There is no backache, since there is no narcosis to induce relaxation of spinal muscles. The dressings may be applied originally to suit the comfort of the patient. Above all, is the advantage gained in being able to operate with comparative safety in patients who would incur immediate risk in submitting to general anæsthesia.

The disadvantages are: The greater time consumed in the operation and the distraction to the surgeon. The operation is doubtless more difficult, and some pain is inflicted. The degree of this depends entirely, however, upon the surgeon's familiarity with the steps of the operation and his knowledge of the anatomical distribution of the sensory nerves of the region. The slight amount of pain that is sometimes met does not compare with the discomforts of the ether convalescence, while the surgeon's difficulties are more than compensated for by his subsequent freedom from anxiety during the period of recovery from the anæsthetic and convalescence.

The Effects of Mechanical Action on Bone Growth.—Maas (*Klin.-therap. Woch.*, 1900, No. 10), in his experiments on young guinea-pigs, found that the long-continued action of pressure or stretching produced an alteration in growing bone both in its outward form and its internal structure. These alterations are not caused by a retardation or an increase in the organic processes of structure building, but by an alteration in the relative positions occupied by the physiological amount of osseous tissue. These alterations result from the action of powerful mechanical agents that overcome the physiological power and alter its direction. Since there is actually no deficiency in the amount of bone produced, when there is a decrease in one direction there must be a complementary increase in another direction

which is free from pressure. The geometrical proportion of the development is thus altered—a decrease in length produces an increase in the thickness. In all the alterations seen in the human body the deformity results from an abnormal relation of the bone-tissue produced and not from a deficiency in the amount produced. These facts contradict the theory of a functional pathogenesis of skeletal deformities and also all inflammatory theories in connection with the pathogenesis of rhachitis.

Traumatic Diastases—WOLFF (*Centralblatt für Chirurgie*, 1900, No. 13) reports the results which the Röntgen rays have shown in the diagnosis of these separations of the epiphysis during the past two and a half years. They have given great precision to the exact differentiation between fractures and true diastasis. He gives special attention to the uncomplicated injuries of the extremities of the long bones. The separation of the epiphysis is, of course, limited by the age of the patient, and is found in patients under eighteen years of age. Thirty-four cases were seen among 525 fractures, 121 only of which were at the age when these lesions occur. During this period their relative frequency, as compared with fractures, is as one to four. The elbow-joint and the epiphysis surrounding it are most frequently the seat of the lesion. They were produced, in general, by direct violence. The dislocation of the fragments is very variable in amount. There is frequently hemorrhage into the neighboring joint. Crepitus is less harsh and pain on pressure less acute than in fractures. When the foci of ossification are small the picture revealed by the Röntgen rays is often indefinite and not easily read. The treatment is in general that of fractures—reposition and fixation. Each lesion is, however, peculiar, and it is here that the knowledge gained from the skiagraph is of great value.

When Shall We Operate in Cholelithiasis?—KOCHER (*Correspondenzblatt für schweiz. Aertze*, April 1, 1900), in answering this question, says: The indication is given by the recurrence of gallstone colic attacks, which show the presence of multiple calculi or of one that is so large that it cannot pass through the bile-ducts or can do so only with great injury to them, or, finally, where a newly-formed calculus is passed. When any of these indications are present we should not wait until secondary changes have occurred and inflammation, with its sequelæ and even perforation, may have taken place, or malignant degeneration has occurred; then recovery is seldom seen.

Is intervention indicated in cases where recovery from the attack is probable and there are no complications? He believes that operation gives the best chance, and is indicated. Simple cholecystotomy is rapidly recovered from, and with perfect technique there is no great danger, and not nearly as much as from the complications that arise from a further development of the disease or the presence of infection. The early operation may remove a great number of calculi, and the ten days required for operation and recovery are well spared when compared with the consequences of repeated attacks.

The ideal cholecystotomy consists in exposing the gall-bladder, opening it, and removing all calculi. It should then be immediately sutured and returned to the abdomen. Such an operation requires absolute asepsis and a perfect suture. The best suture this author believes to be silk. It is in-

serted only in the wall of the bladder, and does not enter the cavity, so the danger of its forming nuclei for other calculi is entirely avoided.

Kocher has performed this operation six times during the winter semester. All the patients recovered, without rise of temperature, in eight days, and were sent home in two weeks' time. This illustrates the simplicity of operation at this early period as soon as the diagnosis is established and before complications have rendered the intervention more hazardous.

He does not believe that any form of medical treatment can remove these calculi or prevent the patient from having recurrent attacks until the calculi are removed. Recurrence is not probable after all the calculi are removed, but the patient should be put upon a regulated diet, with the end in view of preventing the formation of other calculi.

PEDIATRICS.

UNDER THE CHARGE OF

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Pulmonary Affections Consecutive to Infectious Diseases and Gastro-enteritis.—H. SPIEGELBERG (*Archiv für Kinderheilkunde*, 1899, Band xxvii., S. 367) discusses the question of the bronchopneumonias of intestinal origin, which has been sustained by Czerny in Germany, and reaches the conclusion that these bronchopneumonias are to be attributed to secondary infection of bronchial origin.

The researches were made upon 111 children, 90 of whom were one year old, 18 two years old, and 2 three years old. All had succumbed in the course of various infectious diseases, and of the number there were 29 cases of acute, subacute, or chronic gastro-enteritis, with terminal bronchopneumonia.

In all the cases associated with gastro-enteritis the lungs were found to be more or less congested, succulent, and presenting foci of lobular infiltration of variable size. Microscopically these foci were composed ordinarily of bronchioles and alveoli filled with an exudate containing round and epithelial cells. In the severer cases cellular infiltration extended into the alveolar septa and the interstitial tissue, giving a homogeneous appearance to the affected areas. In some cases in which the infectious agents were particularly virulent a superficial necrosis of the mucosa was found.

The mucous lining of the larger bronchi was congested, while that of the smaller branches was covered with purulent exudate, almost completely

filling their lumen. The epithelium was swollen and sometimes was completely desquamated. Cellular infiltration was often observed between the submucous layer and the cartilaginous walls of the bronchi.

In the bronchial and alveolar exudate, in the desquamated epithelium, and in the necrosed areas bacteria were found. They were absent from the bloodvessels, almost always so in the lymph spaces, and were found with no degree of constancy in the tissues. These bacteria were generally the same as were found in the stools. In six cases various bacilli were found, among which the colon bacillus occurred several times; nineteen times micrococci and staphylococci were found, and eight times streptococci (once in pure culture). Pneumococci were observed several times, and in six cases the oïdium albicans.

In the bronchopneumonias consecutive to infections other than gastro-enteritis the lesions compared with those of the preceding group presented the following peculiarities: more frequent and extensive infiltration of the interstitial connective tissue, in which the bacteria appeared massed together in clumps; relative integrity of the epithelium of the bronchi; cellulo-serous or fibrinous character of the exudate; and an intensity of capillary hyperæmia going on to the production of hemorrhages. In this group there were found bacilli in five instances; cocci in six (once staphylococci and streptococci alone, and these in association with others in the other cases); and pneumococci in four.

Histological and bacteriological examination of the intestines in the children of the first group, as to the possibility of passage of bacteria by lymphatics or bloodvessels, gave negative results. Almost always bacteria were found on the surface of the mucous membrane and about the excretory ducts of the glands; in the submucous tissue ulcerations were found, but never bacteria in the lymphatic apparatus or in the mesenteric ganglia.

In seven cases the blood was examined during life; it was found sterile in four cases, and contained streptococci in three; but in these three cases the port of entry was certainly not the intestine.

The author, therefore, concludes that in the immense majority of cases bronchopneumonia occurring in the course of gastro-enteritis is due to a bronchogenic infection.

Extract of the Suprarenal Capsules in the Treatment of Rhachitis.—W. STOELTZNER (*Jahrbuch für Kinderheilkunde*, 1900, Band i., S. 73 and 199) has made an extended study in Heubner's clinic of the action of suprarenal extract in rhachitis. The following is a *résumé* of his conclusions:

1. Suprarenal extract exercises a very favorable action upon the general state, the agitation, the perspiration, the vasomotor excitability, and especially the craniotabes of rhachitic infants. All these symptoms are often considerably ameliorated within eight to fifteen days.

2. Children thus treated rapidly become able to walk, to run, and to sit upright; the softness of the bones of the thorax disappears very rapidly, and the delayed teeth begin to appear.

3. The dimensions of the fontanelles, the deformity of the thorax, the costal rosary, the epiphyseal swellings, and the deformity of the limbs are little influenced.

4. Spasm of the glottis almost always resists this treatment.

5. The amelioration of all the symptoms is especially manifest during the first eight days of treatment; later it is much less rapid.

6. If the treatment be interrupted improvement ceases, or there is actually an aggravation of the condition, which yields when the treatment is begun anew.

7. Even in the cases complicated by syphilis, enteritis, bronchitis, or bronchopneumonia, treatment by suprarenal extract produces considerable amelioration of the rhachitis.

8. In a case of grave rhachitis treated by suprarenal extract, in which death was caused by a capillary bronchitis, the histological examination of the bones showed that there were no traces of osteoid tissue, and that even the periosteal osteophytes gave an almost complete reaction of calcified osseous tissue.

Parotitis, with Involvement of the Submaxillary Glands.—J. HOPPE (*Münchener medicinische Wochenschrift*, 1899, No. 34) has observed among children of the asylum of Uchtspringe an epidemic of mumps which was peculiar in affecting the submaxillary glands instead of the parotids. Sixteen cases were observed. Of these 10 began by a swelling of the left submaxillary gland and 6 of the right. In 8 cases (50 per cent.) the submaxillary of the opposite side was involved in turn from one to nine days after the onset of the disease. In 6 cases there was secondary involvement of the parotid gland two to three days after that of the submaxillary. Swelling disappeared usually in from ten to fifteen days. Three boys complained of testicular pain. There were no other complications.

Treatment of Chronic Constipation in Childhood.—H. DOERFLER (*Münchener medicinische Wochenschrift*, January 23, 1900) speaks very highly of the treatment of this often perplexing condition by the administration of butter. This should be perfectly fresh and of the best quality, and should be given pure without any vehicle. During the first month of life constipation is quite unusual and may be controlled by enemata. In the second and third month one-half to one coffeespoonful of butter may be given daily, morning and evening, until the stools are normal, then every second day. In the third and fourth months two to three coffeespoonfuls daily may be given, with a decrease in dosage after the stools have become normal. From five or six months to a year, one to three teaspoonfuls may be given every two or three days.

The Elimination by the Urine of Sugars Introduced Subcutaneously or by the Digestive Tract.—NOBÉCOURT (*Revue Mensuelle des Maladies de l'Enfance*, April, 1900, p. 161) calls attention to the fact that while the conditions which regulate absorption, assimilation, and elimination of various forms of sugar have been thoroughly studied in the adult, very little work of the kind has been done with infants. He has, therefore, undertaken an investigation of the subject with reference to the first three years of life, and has deduced some interesting conclusions. He finds that the intestinal

mucous membrane of the child has the power of transforming large quantities of lactose introduced into the intestine with the milk, and is capable of transforming single doses considerably larger than those contained in an ordinary nursing of mother's milk. In general this power is greater in the young child than in the adult, but there are numerous exceptions.

For saccharose the intestinal mucosa has an inverting action fully equal to that exhibited toward lactose. In comparing the two it is necessary to take into account the strength of the dilutions; for equal degrees of dilution the action of the intestinal mucosa appears to be equal for the two sugars. Glycosuria was never observed in healthy infants experimented upon with lactose and saccharose, but in some rhachitics alimentary glycosuria was produced with glucose.

For glucose the organism of the young child has a much more marked action than has that of the adult. This action does not seem to be limited to the liver, but extends to all the tissues.

Acute Serous Meningitis and Seropurulent Meningitis Due to Streptococci.—An instructive contribution to the pathogenesis of meningeal inflammations occurring in the course of acute diseases is made by NOBÉCOURT and DELESTRE (*Annales de Médecine et Chirurgie Infantiles*, April 15, 1900, p. 261). During an epidemic of bronchopneumonia in the service of Hutinel at the Hospice des Enfants-Assistés two cases were observed, both terminating fatally, one of which presented the lesions of an acute serous cerebral meningitis, the other of a seropurulent cerebro-spinal meningitis, in both of which the same organism—a streptococcus—was found.

The first case was an infant, aged twenty months, admitted for bronchopneumonia. Five days after admission meningeal symptoms appeared: rigidity of the neck, vomiting, Kernig's sign, strabismus, irregularity of the pulse and respiration, cerebral tâche, and moderate elevation of temperature. Seven days later a measles eruption appeared coincident with an amelioration of the cerebral symptoms, but the pulmonary condition became aggravated, and death occurred on the following day. At the autopsy, in addition to the lesions of bronchopneumonia, there was observed a diffuse, œdematous congestion of the meninges of the convexity of the hemispheres, more marked posteriorly. The cerebro-spinal fluid was abundant, but clear and limpid, as was also that of the lateral ventricles. There was no solid exudate and no tubercles. The spinal meninges were unaffected. Cultures of the cerebro-spinal fluid, obtained by lumbar puncture during life and also at the autopsy, showed the presence of a streptococcus (pure).

A second case observed in a child, aged four years, who had presented meningitic symptoms for two days before death, showed at autopsy the lesions of a seropurulent cerebro-spinal meningitis. The cranial meninges were distended by a cloudy, whitish fluid rich in leucocytes. Upon the convexities the meninges were infiltrated with an opalescent exudate, especially marked about the sulci and fissures. The fluid of the lateral ventricles was abundant and cloudy. The spinal meninges at the lumbar enlargement contained cloudy fluid, and the posterior aspect of the cord at this point presented an opaline appearance. Bacteriological examination of the cerebro-spinal fluid from the lateral ventricles and from the lumbar por-

tion of the cord showed the presence in pure culture of a streptococcus analogous to that observed in the first case.

The same organism, therefore, determined in one case a serous inflammation, in the other a seropurulent one. In discussing the reason for this difference of effect the authors think that a difference in the virulence of the germ in the two cases can scarcely be invoked, since in the seropurulent case the organism was innocuous for animals; neither could the duration of the disease be considered important, since the serous inflammation evoluted more slowly than the other. The hypothesis of a special resistance or a peculiar predisposition of the meninges alone remains, but these are factors which are not clearly understood.

The organism presented some interesting peculiarities. It grew poorly at first upon gelose, giving very minute punctiform colonies, resembling those of the pneumococcus. After several removes it acquired the typical characteristics of a streptococcus, giving in liquid media a deposit formed of large clumps. Morphologically it had at first the form of a diplococcus; later there were long chains when cultivated in the blood-serum of the rabbit. The organism possessed no capsule taking stain. It was virulent for neither rabbits nor mice.

THERAPEUTICS.

UNDER THE CHARGE OF

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Atmokausis.—Dr. A. von Guérard reports his results from the use of this method in twenty-one instances. For uterine hemorrhage, especially at the climacteric, this method is serviceable. The results in putrid abortion, endometritis, carcinoma, and dysmenorrhœa are uncertain. It was successfully used in a bleeder whose mother and sister had died from hemorrhage. The application was made at 239° F. for thirty seconds Of these twenty-one patients seventeen suffered pain, in five of whom it was excessive, and this symptom was accompanied by fever. This method may be used successfully when contraindications exist to others.—*Therapeutische Monatshefte*, 1900, Heft 3, S. 154.

Soluble Silver.—Dr. A. Dwaretsky reports the histories of two patients suffering from phlegmon of the hand, with septicæmia, one of the same condition of the foot, one of furunculosis with septic infection, and one of chronic osteomyelitis of the femur, with chronic septicæmia. In all inunction with the ointment was practised, and this resulted in benefit both to the local sepsis and the general septic conditions. These instances of its use fully confirm the claims of Credé and others.—*Therapeutische Monatshefte*, 1900, Heft 3, S. 145.

[Soluble silver has apparently secured a permanent position in the treatment of general sepsis.—R. W. W.]

The Treatment of Scarlet Fever Nephritis.—Dr. Wertheimher pleads for the methodical use of intestinal irrigation with physiological saline solution as an important adjunct to treatment. This increases diuresis and militates against or prevents uræmic symptoms. Although this acts by increasing the flow of urine, this is not its only valuable function.—*Klinisch-therapeutische Wochenschrift*, 1900, No. 11, S. 338.

Asthma and its Treatment.—Dr. G. A. Gilbert bases treatment on the statements of Haig and others that the contraction of the bronchi and arterioles is often due to the accumulation of uric acid in the blood. The biurate crystals, by their points, set up a reflex irritation of the terminal branches of vagi in the bronchial mucous membrane. Frequency of attacks is in proportion to amount of uric acid. Permanent relief follows a sufficient elimination of the poison. It is noted that the paroxysms usually occur in the early morning, when the amount of uric acid is greatest, and that after an attack there is a flow of limpid, pale urine in great quantity. Thioline, the laxative salt of lithium, forms in the system the freely soluble lithium urate, which is completely eliminated by the emunctories. Potassium iodide forms urate of potash, which is only partially soluble. In addition to its solvent hydrogen action, thioline relieves arterial tension markedly, which condition always accompanies true bronchial asthma.

Method of administration: A teaspoonful in a cup of hot water every three hours until free catharsis results; thereafter the same dose is given once a day on rising. When urine is alkaline, medication is omitted for two days. In addition the diet is to be limited, strongly nitrogenous food being interdicted. Under such treatment very satisfactory results are reported; patients who have been subject to attacks for years remaining free therefrom for months at a time.—*St. Louis Medical and Surgical Journal*, 1900, vol. lxviii., p. 125.

[Our observations tend toward the opinion that in asthma we have much more than uric acid as a prevalent causative factor. As for the value of the drug mentioned, we have found it neither more nor less valuable than other lithium salts and mixtures.—R. W. W.]

Kryofin.—Dr. Albert Breitenstein has employed this remedy chiefly as an analgesic, especially for headaches. An instance of migraine which had resisted long-continued medication was relieved by two seven-grain doses of this drug. It is also an excellent remedy for the headache of acute alcoholism. Recent sciatica, lumbago, intercostal neuralgia, and pleuritic pains are subdued by fifteen-grain doses. Insomnia in neurotic individuals is controlled. The remedy is safe and certain in its action, and does not give rise to untoward symptoms.—*Therapeutische Monatshefte*, 1900, Heft 3, S. 137.

Untoward Symptoms from Pyramidon.—Dr. W. Pauli reports two instances. After five five-grain doses there was noticed painful paræsthesia of both forearms, which radiated into the fingers and increased in severity on the

following day. Three similar cases of this dosage resulted in sleeplessness. On cessation of the remedy these symptoms disappeared, to return on a repetition of the dose. The second patient showed over the face, neck, arms, joints, and chest an eruption which resembled urticaria. Upon the face these spots became confluent, and later resembled the eruptions of measles. —*Centralblatt für die gesammte Therapie*, 1900, Heft 3, S. 129.

Mercurial Neuritis.—Dott. P. C. Madinos reports an instance in which the pains were most marked in the knees and ankles. These were acute and lancinating and especially aggravated by any movement. Later the patellar reflex became weaker and tactile sensibility slightly blunted, while that of pain and temperature was normal. Soon œdema reaching to the knees set in, and finally fever became constant. At this time it became apparent that the mercurial inunctions which the patient was receiving were responsible for the symptoms, and not the syphilis for which he was receiving them. Intestinal antisepsis was secured with benzonaphthol and salol. Hot salt baths were administered and occasionally morphine hypodermatically for severe pain. Within a fortnight the œdema disappeared, the pain gradually lessened, and total relief came ten days later, and the patient recovered full use of his limbs. Attention is called to the fact that mercurial neuritis has not been thoroughly studied and that there is likelihood of attributing the symptoms to the disease and not to the remedy employed for it.—*Gazetta degli Ospedali e delle Cliniche*, 1900, No. 24, p. 252.

Creolin in Eczema, Psoriasis, and Other Diseases of the Skin.—Dr. David Walsh states that the main action of this substance is that of a mild, deodorizing antiseptic, while, in addition, it is a vascular stimulant and absorbent in dry skin diseases, and as a nervous sedative in many sensory cutaneous disturbances. In eczema and other acute inflammatory conditions a drachm to a quart of warm water may be sponged over the parts two or three times daily, followed by a dusting powder of zinc oxide. As the inflammatory condition subsides an ointment of creolin and vaseline (1 : 16 or 48) may be employed. This is useful for rubbing into the dry patches of psoriasis. If there is much scaling salicylic acid should be added. For all but the acute catarrhal inflammations a bath of hot water, to which a drachm of creolin is added for each gallon, is excellent. Friction should be vigorously employed. As an antipruritic a drachm to a pint of hot water, to which a few drachms of glycerin is added, gives much relief in the distressing pruritus of the aged.—*The Therapist*, 1900, No. 3, p. 62.

The Treatment of Obesity.—Dr. E. Heinrich Kisch finds that the continued use of purgatives is quite as much to be condemned as the former employment of blood-letting. Their use results in increased peristalsis and diminished absorption from the intestines, resulting in lessened nutrition and not in removal of fat. Noting the action of alkalies on fats producing soap, various authors have recommended large doses continued over considerable periods of time. Inasmuch as laboratory research shows that the result is merely a lessening of oxidation-processes, it is difficult to believe that it is efficient. Vinegar from various sources has been a popular domestic

remedy, but readily gives rise to a cachexia with various dyspeptic symptoms. Various preparations of iodine diminish flesh, but give rise to prostration and even to symptoms of iodism, as nervous unrest, insomnia, dyspnœa, palpitation. Anæmic patients should not be submitted to this treatment. Plethoric individuals, however, may be given small doses for short periods. Often local applications are useful: the size of the breasts and abdomen may be reduced by inunctions of iodine or iodide ointments; potassium iodide, 10; iodine, 1; petroleum ointment, 100. The use of diaphoretics in the treatment of obesity dates back to Galen. Of all methods the hot bath, due regard being paid to the condition of the heart and arteries, is the most useful. Recently thyroid preparations have been much lauded, although the results are not constant, and cessation of the treatment is likely to be followed by increase of weight. Their disadvantage lies in the fact that not only is the fat lost, but the albumin as well; if strict diet is not enforced in plethoric patients only moderately good results may be looked for and only exceptionally any untoward symptoms. In anæmic patients rapid loss of weight occurs and also marked cardiac and nervous symptoms, which prevent the long continuance of the remedy. If treatment at Marienbad is carried on simultaneously in plethoric patients no other effects are observed other than those from the Marienbad treatment alone excepting a more rapid appearance of prostration. If thyroid preparations are employed untoward symptoms on the part of the heart, nervous system, blood and kidneys should be looked for and the remedy stopped or diminished. In all cases the initial dose should be small and only gradually increased.—*Therapeutische Monatshefte*, 1900, Heft 2, S. 75.

Treatment of Pleurisy.—Dr. G. Debove recommends counter-irritants applied to the chest on the affected side, especially over the site of pain. Both dyspnœa and pain are lessened thereby. Wet cupping is indicated only when the pain is very severe. Leeches, dry cups, sinapisms, and cauterization are ordinarily effectual. Blisters are to be avoided as dirty and not devoid of danger (sepsis); further, they do not aid in the absorption of the effusion. Diuretics do not cure a pleurisy, and may have an injurious effect on the kidneys. Rational treatment consists in thoracocentesis. Age is not a contraindication. When the fluid does not exceed a pint the operation is unnecessary. Greater effusions demand it, proportionally to their size, and especially if there be dyspnœa. To avoid syncope the horizontal position during operation is preferred. Potain's or Dieulafoy's aspirator is satisfactory, and a fine needle is better than a trocar and canula. Ordinary rules of aseptic operating apply. To avoid possible injury to the intercostal artery and nerve, it is well to keep close to the upper margin of the rib in introducing the needle; the fifth space in the mid-axillary line is the point of election, for here the ribs are far apart and there is no danger of puncturing the diaphragm. Accidents following thoracocentesis are: rapid reproduction of the fluid, its purulent transformation and albuminous expectoration. Return of the fluid is due to persistence of the original cause of the pleurisy, and not to the operation. When there is recurrence a tuberculous origin is probable; such effusions easily become purulent. Liability to purulent transformation is a great drawback to thoracocentesis. It is added that many

effusions spontaneously become purulent. Albuminous expectoration follows too rapid an evacuation of a large amount of fluid. Mild degrees involve dyspnœa with continuous expectoration and cough. More severe forms include abundant expectoration with intense dyspnœa, and auscultation shows œdema of the lungs. Asphyxiation may follow. Albuminous expectoration is apparently due to congestion of the lung with acute œdema and serous invasion of alveoli. To avoid this more than one quart of fluid should never be removed at one time. A second puncture may not be required, for often small amounts of fluid remaining in the duct are rapidly absorbed. Pneumothorax is not a dangerous complication. Syncope, due to a too complete and sudden evacuation of the fluid, causes rapid congestion of the lung and consequent anæmia of the medulla. Thoracic pain is probably due to distention of the pleura when the compressed lung returns to its normal volume.—*The Medical Press and Circular*, 1900, vol. cxx., p. 181.

Diabetes Mellitus of Apparent Bacterial Origin Successfully Treated.—Dr. J. P Sheridan made use of mercuric chloride and failed to produce any good effects. A similar result followed the taking of gold and sodium chloride. Failure is ascribed to: 1. The specific toxin of diabetes is affected only by a specific antiseptic. 2. The above drugs when pushed to the point of intolerance do not cause a decline in glycosuria. 3. Both drugs, administered for any length of time and in large doses, reduce the oxidizing power of the red blood-cells, weakening the system, and causing rapid emaciation. In the writer's hands a preparation of gold and arsenic bromides in solution, in four instances excited an apparently specific effect on the bacteria and toxins of diabetes mellitus. The combination is given, largely diluted in water, beginning with eight to ten drops, thrice daily, and slowly increasing to the limit of toleration, usually between forty and sixty drops. The indications that the point of toleration has been passed are as for arsenic in general: swelling of the lids, puffiness of the face, diarrhœa, etc. When this point has been reached the dose is reduced five or ten drops, and thus continued for several months. Improvement in all four cases was immediate and constant. After some weeks had elapsed glucose wholly disappeared from the urine, and other symptoms likewise vanished. There was no subsequent return of symptoms. In each instance it was recommended that the patient continue to take the drugs recommended for at least six months. In addition to medication restriction of diet is advised, with reference to sugar and starches.—*New York Medical Journal*, 1900, vol. lxxi., p. 236.

The Serum Treatment of Diphtheria.—Dr. A. Anderson shows that the mortality before antitoxin was introduced was everywhere exceedingly high. The results of comparison are: As high as 42 per cent. mortality previously (Sheffie'd), and as low as 6.77 per cent. subsequently (Chicago). It may be stated that the character of the disease has altered, being less virulent than formerly, and that more throat affections are recognized as diphtherial than heretofore. It is extremely unlikely that so virulent a disease should have become benign in so few years. Statistics show that older methods had comparatively little effect on the death-rate, whether first coming under treatment on the first or the fifth day. There is a direct relation, however, between re-

covery and the early administration of antitoxin. Series grouped according to age show a striking diminution in mortality for younger children, who are ordinarily more susceptible to the disease. One of the first effects of the administration of the antitoxin is the rapid disappearance of the membrane and the extreme rarity of further extension of the lesion. Especially is this important in laryngeal diphtherias. Formerly the death-rate for this form of the disease was 60 per cent. During 1898 it was 34 per cent., antitoxin being used. In patients requiring tracheotomy the mortality has fallen from 70 to 30 per cent. Operative interference is also less often required. Involvement of the larynx subsequent to the appearance of the membrane in the nose and pharynx indicates a late stage of the disease and that the patient has not received antitoxin. Such patients die from cardiac failure, anuria, or paralysis. Laryngeal symptoms never supervene in diphtheria where antitoxin has been already injected. Still more satisfactory results follow in post-scarlatinal diphtheria. In a certain proportion of instances complications may be caused wholly by the serum. Urticarial and erythematous rashes occur, appearing a fortnight after injection. Abscesses form in 2 per cent. of patients injected. No serious constitutional disturbance nor sloughing have been observed by the writer, and those described are probably due to some extraneous organisms in the serum; therefore, any serum that has become cloudy should be discarded. Arthritic symptoms are painful, never serious. They are more common in adults. Occurrence of albuminuria and paralysis has increased since the introduction of antitoxin; almost all severe albuminurias appear when the antitoxin has not been administered until the fifth day or later. Paralysis has increased because more patients survive to develop it than formerly. When the injection is made early paralysis is infrequent, and is mild, as a rule. The dose of the serum depends on the severity of the injection, not on the age of the patient. Early diagnosis means a small dose. Four thousand units are considered a mild dose. In severe infections four thousand units should be given every three hours, for three doses, and repeated the following day if necessary. Large doses may thus be given with impunity. To determine the necessity for a repetition of the dose, examine the false membrane. If nasal discharge was present and it has entirely ceased, injections may be discontinued. Absence of nasal discharge and a sodden appearance of the membrane, with a well-marked loosened edge indicates that little more antitoxin is required. The temperature-chart is unreliable, though fever usually diminishes in uncomplicated lesions. It is better to repeat such doses as above given than to give larger initial injections. That four thousand units is always sufficient is untrue. The aim is to neutralize the toxin before it destroys the nerve and other cells. Antitoxin has no bactericidal effect; toxins continue to be elaborated until the tissues have themselves overcome the bacteria. If the bacteria pass into the general circulation the area for the elaboration of toxins is enormously increased, and these latter must be neutralized by correspondingly large doses of antitoxin. Injections must be given at the earliest possible moment. It is best not to wait for the result of a bacteriological examination. In judging of the severity of an attack account must be taken of the susceptibility of the patient and of the virulence of the bacteria. As there is no accurate way to judge these

factors, every patient should receive antitoxin whether the symptoms appear mild or not. Paralysis and other grave complications arise as often in the apparently mild injections as in the more severe. Local treatment is also requisite. Cervical cellulitis is common in the more severe attacks. Antistreptococcic added to antitoxic serum in such a condition gives no better results than antitoxin used alone. A serum from which the elements causing the rashes and joint pains are eliminated, as well as one of greater strength, is desirable. Whether cells partially destroyed by toxin can be restored to their normal state is problematical.—*The Quarterly Medical Journal*, 1900, vol. viii. p. 173.

Typhoid Fever in Children Treated by Cold Baths.—GLÉNARD reviews the writings of many authors, and adding his own experience, concludes that cold bathing is of great value. Typhoid fever is a serious illness in children. When treated by medicines alone the mortality amounts to 15 per cent. When cold bathing alone is used the mortality is 2.5 per cent. A combination of medicines and cold baths, the latter used as a *succedaneum*, results in 11 per cent. mortality. When both internal medication and baths are employed the prognosis is uncertain, complications are prone to occur even in most mild attacks, the duration is prolonged, and convalescence likewise. Systematic treatment with cold baths brightens the prognosis after the first few days, complications are reduced to a minimum, convalescence is short, and a persistence of sequelæ rare. Collapse, as a result of cold bathing, is also rare, and this is true, too, in pneumonia in infants treated in a similar manner—a disease in which the heart is most menaced. It is neither too cold nor too prolonged a bath that causes collapse, but delay in instituting this method of treatment, or an advanced stage of the disease with the lack of cardiac stimulants, when they are evidently required; under such conditions collapse following bathing does occur. Because the cold bath is not made the basis of treatment, collapse often occurs in patients treated both by drugs and by baths. Following is the method of bathing: Temperature of water, 72° F.; duration of bath, ten minutes; "cold affusions," thrice repeated. To be repeated every three hours as long as the rectal temperature taken just before the bath is 102.2° F. When the fever ranges between 100.4° to 102.4° F. the bath should be given for as many minutes as the thermometer registers fifths above 100.4°. If the heart weakens a drachm or two of Bordeaux wine is indicated before and after the bath. Should collapse threaten, cold affusions are required, the bath is shortened, friction of the surface and massage are practised during the bath, and warmth applied subsequently. Subcutaneous injections of ether may be necessary. In any case as long as the temperature before the bath is 102.2° F. bathing is indicated. Each bath renders collapse less likely. The author believes that the results of treatment by the Brand method are even more satisfactory in children than in adults. In children thus treated typhoid fever is a very benign disease, and it is so only when thus treated.—*Revue de Thérapeutique*, 1900, No. 3, January 15, pp. 37 and 73.

Benefits of Balneotherapy in Chronic Rheumatism and Gout.—DR. H. H. SCHROEDER writes: It has been demonstrated that if a mammal be

placed in a bath three or four degrees higher than its own temperature excretion of carbon dioxide gas and consumption of oxygen are increased, owing to the stimulation of metabolism; urea is also excreted in large quantities. This latter increase continues for several days after a series of hot mineral-water baths. Stimulation of the cutaneous sensory nerve exercises an important influence on the most complicated processes, by means of reflexes through the central nervous system. Anything tending to intensify the stimulation of the peripheral nerves will favor greater functional activity. Probably the best results are obtained from treatment at those springs with temperatures considerably over 100° F., and containing high percentages of mineral ingredients. During immersion in such waters pathological products, exudations, hyperplasias and toxins are "drawn into solution" and eliminated from the system. Care must be used in the choice of patients for such treatment. Chronic nephritis complicated with arterio-sclerosis or hypertrophied left ventricle, valvular heart lesions, etc., are contraindications. Well compensated valvular lesions unaccompanied by renal or vascular complications suffer no inconvenience. Chronic rheumatism has usually progressed so far that thickening of the synovial and periarticular tissues has occurred. Anchylosis often follows. During these chronic stages of rheumatism balneotherapy persisted in will generally meet with gratifying results. As patients are usually in run-down condition, drastic measures are to be avoided. Natural spring waters, of high temperatures, containing much mineral matter, are best for stimulating absorption. Massage and douches are also serviceable. In gout the establishment of a more complete metabolism and the elimination of uric acid, in addition to the absorption of deposits about the joints, are to be sought for. Whatever may be the relation of uric acid to gout, measures that favor its elimination and prevent its formation are valuable in treatment. Life at a mineral-water bathing resort is conducive to this end; habits are regulated and a proper diet enforced.

Irksome treatment is willingly submitted to. Living in a pure atmosphere and taking abundant exercise, hot sulphur springs containing sodium chloride and alkaline and earthy sulphates tend to remove the various disorders in causal relationship to gout, such as indigestion, gastric and intestinal catarrh, and constipation. Senator believes that such waters exert an immediate influence on the gout diathesis, and uric-acid dyscrasia, and that permanent benefit is derived from their influence. Increase of pain often accompanies the bath. It soon ceases, as a rule. With its disappearance comes that of the disease, and immunity follows for some time if not permanent cure.—*New York Medical Journal*, 1900, vol. lxxi. p. 269.

The Use of Guaiacol in Malaria.—Dr. Charles J. Whalen reports twelve instances of the use of this remedy. In nearly all quinine had been used, and it had failed to cure. The dose is five drops after meals, increasing one drop each day until twenty drops three times daily are taken. From these observations he infers that the adult segmenting organism is not affected by the drug, but the free and growing spores constantly inhibiting nourishment from the blood-plasma are readily destroyed or prevented from entering new corpuscles.—*Merck's Archives*, 1900, No. 4, p. 133.

GYNECOLOGY.

UNDER THE CHARGE OF

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Œdema of the Bladder Due to Stricture.—KOLISCHER (*Centralblatt für Gynäkologie*, 1900, No. 17) believes that strictures of the urethra in the female may be of congenital origin, being independent of any previous inflammatory process. They are caused by localized deposits of fibrous elastic tissue, and are only recognized clinically by using olive-pointed bougies. When seen through the endoscope they appear as semicircular or circular ridges around the canal. While in some cases they give rise to no symptoms, in others the patient complains of constant irritation and tenesmus, while the urine contains numerous epithelial cells and detritus. Cystoscopic examination of the bladder in these cases shows œdema of the mucous membrane at the neck of the bladder, which may involve the mucosa generally. Instead of presenting the usual deep-red color, it is pale and swollen, resembling wet absorbent cotton.

In many instances, through diminished vitality of the mucosa or actual infection, there may be an actual loss of substance over the œdematous area, which in time results in the formation of an ulcer. Treatment is useless as long as the presence of the stricture—the true cause of the œdema—is unrecognized. Internal urethrotomy followed by applications of iodoform to the ulcer effects a cure.

In conclusion, the writer insists upon the importance of a thorough cystoscopic examination in young women with obstinate vesical symptoms, even though the usual etiological factors—gonorrhœa and puerperal lesions—are absent.

Abnormal Openings of the Ureters.—BENCKHISER (*Zeitschrift für Geb. u. Gyn.*, Band xli., Heft 3) adds two cases to the twenty-five already reported. In one a ureter opened below and to the outer side of the meatus; in the other an accessory left ureter opened in a similar locality. In the first case, after extirpating the lower end of the ureter, a fistula was left in the upper third of the vagina; in the second the lower portion of the accessory ureter was extirpated and the upper portion was turned into the bladder.

OLSHAUSEN (*Ibid.*) describes two additional cases, one in a child, aged ten years, in which the opening of the right ureter was situated near the right edge of the hymen. The absence of the right uterine opening in the bladder was demonstrated by the cystoscope. In the second case the opening of an accessory ureter was found near the meatus. The distal end was resected and an unsuccessful attempt was made to suture the proximal end in the urethra. Eventually a successful anastomosis with the bladder was effected.

Treatment of Incontinence of Urine.—ZIEGENSPECK (*Deutsche Arztezeitung*, 1900, Heft 14) summarizes the treatment of incontinence (when not due to fistulæ, cystitis, or parametritis) as follows: 1. Massage of the urethra and neck of the bladder, according to Brandt's method. 2. Dilatation of the vesical sphincter with sounds, as suggested by Sänger. 3. Suture of the sphincter muscle by introducing a sound into the bladder to serve as a guide, and then passing a silkworm-gut suture around the urethra and neck of the bladder, the suture being tied in the vagina and left *in situ* for eight or ten days. 4. Resection of the sphincter muscle, by cutting down upon a sound as a guide, excising 0.5 cm. of the muscle, and suturing the ends with fine catgut, a catheter being left in the bladder.

[No mention is made of the use of the faradic current, which is a valuable agent for restoring the tone of the relaxed sphincter muscle, and ought certainly to be tried before resorting to the cutting operation.—ED.]

Angiotrypsy.—RATCHINSKY (*Revue de Gyn. et de Chir. Abdom.; Centralblatt für Gynäkologie*, 1900, No. 17), from experiments on animals, finds that while the lumen of the compressed vessel is occluded, the adhesion of the intima is not invariable, while the tunica externa has a tendency to return to its former condition, thus allowing subsequent hemorrhage. He concludes that while complete hæmostasis is possible with the use of the angiotribe, in some cases it is only temporary. In vaginal hysterectomy secondary hemorrhage is not infrequent, and may even necessitate abdominal section. Further experience with the instrument is necessary. The use of the heavier models is attended with considerable danger.

Results of Castration.—ALTERTHENN (*Hegar's Beiträge zur Geb. u. Gyn.*, Band ii., Heft 1) reports the results of his observation in 107 cases of double oöphorectomy, including twenty-four cases of supravaginal amputation of the uterus.

Complete cessation of menstruation occurred in all the cases of supravaginal amputation. In 55.5 per cent. of the others the menopause was established at once; in 25.8 per cent. hemorrhages persisted for different periods, but eventually ceased. In 18.7 per cent. menstruation still continued. Menstrual molimina ceased with the cessation of the flow. Postclimacteric phenomena were almost constant, although they were less frequent and severe after supravaginal amputation with removal of the adnexa. Diminution of sexual feelings was noted in over 68 per cent. Increase in hairy growth and pigmentation was not observed, and only once a change in the voice. An increase in the body weight was noted in 29.5 per cent.

Involution of the vagina and external genitals (contraction, stricture, etc.) was quite constant. When uterine fibromyomata were present they diminished in size in 97 per cent. of the cases.

In conclusion, the writer infers that the importance of conservative treatment of the ovaries has been overestimated. He is opposed to the view of Abel and Schmitz, that the ovaries should be preserved in cases of myomotomy, since experience has shown that a second cœliotomy may be necessary in order to remove them.

[So much has been written in unqualified support of the practice of pre-

serving portions of ovaries that it is well to have some evidence on the other side of the question. While the practice of conservative surgery is most commendable, it is only fair to state that conservatism has often been carried too far, a second operation being necessary to restore the patient to health.—ED.]

Pyosalpinx with Vaginal Atresia.—GODART (*Policlinico; Centralblatt für Gynäkologie*, 1900, No. 17) reports the case of a married woman, aged twenty-five years, with painful and scanty menstruation, whose vagina was less than three inches in depth, ending in a cul-de-sac. As a small, adherent uterus could be felt per vaginam, the os was exposed by blunt dissection, and dilatation and curettement were performed, after which the abdomen was opened. An adherent pus-tube was removed and the uterus replaced and sutured in position. The left tube was healthy. Pus from the tube contained staphylococci, the origin of which was unknown, as it did not seem possible that they could have penetrated from without, in view of the congenital atresia of the vagina.

Prevention of Conception.—In a discussion of this delicate theme before the Hamburg Obstetrical Society (*Centralblatt für Gynäkologie*, 1900, No. 18) various methods were proposed, none of which appeared to be certain. Objections were made to so-called occlusive pessaries, since they frequently gave rise to endometritis, and were harmful in cases of inflammatory disease of the pelvic organs. It was agreed that under some conditions the physician was justified in trying to prevent conception.

In cases of extreme pelvic contraction, tuberculosis, and other wasting diseases it was advised that ligation or resection of both tubes be practised when the abdomen was opened for other reasons.

Mortality After Cœliotomy for Tubercular Ascites.—WUNDERLICH (*Archiv für Gynäkologie*, Band lix., Heft 1) utters a warning against indiscriminate operations for tuberculosis of the peritoneum. Analyzing 500 cases, he finds that 68 per cent. were of the exudative variety, 27 per cent. the fibro-adhesive, and 4 per cent. purulent. Two-thirds of the first class were observed at least three years, and in 23 per cent. of these the ascitic fluid accumulated rapidly after operation. In the 344 cases of the exudative variety the primary mortality was 22.6 per cent.; 23 per cent. were well three or more years after operation. Operations were most unfavorable in the suppurative variety, over 50 per cent. succumbing at once or a short time after.

The writer has no doubt that abdominal section has a favorable influence upon tuberculosis of the peritoneum, but would not go so far as to affirm that it is the only and certain means of effecting a cure. Spontaneous cure undoubtedly occurs, and it is possible, as Galti and Hildebrandt believe, that the most successful results are obtained in cases in which retrograde processes have already begun in the tubercular nodules when the abdomen is opened. Cases for operation should be carefully selected. Simple ascites without complications offers the best prospect of a permanent cure.

OBSTETRICS.

UNDER THE CHARGE OF

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The Pathology and Symptoms of Degeneration of the Chorion.—In the *Transactions of the Obstetrical Society of London* for 1899, p. 303, WILLIAMSON reviews briefly the early writings upon the pathology of this condition. Hydatid degeneration of the chorion is believed to be closely allied to the myxoma fibrosum described by Virchow. It is thought that the degeneration of the chorion precedes the death of the embryo, as might naturally be expected. Williamson doubts the fœtal origin of the hydatid disease, and quotes cases of repeated molar pregnancies occurring in the same woman.

The frequency of this condition is thought to be one in twenty-four hundred pregnancies. Hydatidiform pregnancy may occur at any time during the child-bearing period, the age of the woman having very little influence. It is more frequent in those who have borne few children, and in these patients previous pregnancies have not followed each other with great rapidity. The usual symptoms of pregnancy are present excepting uterine souffle and fœtal heart sounds, although occasionally these are heard. The one sign which is constantly present is enlargement of the uterus.

In diagnosticating the condition we find some cases in which the uterus is larger than would be expected from the probable duration of pregnancy. In the second class of cases the womb is considerably smaller. Uterine tenderness is generally present.

Another diagnostic point is discharges from the vagina, with or without cystic material. The third diagnostic point is the occurrence of hemorrhage.

We must separate in diagnosis from this condition concealed accidental hemorrhage and placenta prævia, and the discharge of a pelvic hydatid through the vagina, and also polyhydramnios, especially if combined with hydrorrhœa gravidarum.

In the treatment of these patients albuminuria is a frequent complication. In one form of albuminuria blood and epithelial casts are not present in the urine. In the other these structures are found during the pregnancy. Another complication is hemorrhage, which is seldom fatal in itself. The third complication is septic infection in the form of sapræmia, septicæmia, and pyæmia. This, unfortunately, is of frequent occurrence and demands careful consideration. The mortality of the twenty-five cases which Williamson has collected was 20 per cent. The mortality of ten consecutive cases from St. Bartholomew's Hospital was 30 per cent.

[A most interesting point was brought out in the discussion by Fraenkel, of Breslau, in which he stated that according to recent researches hydatidiform mole is not a true myxoma, but a myxomatous degeneration of stroma, with very active growth of the epithelium of the villi. It is essentially

a chorio-epithelioma benignum. If retained remnants of a mole undergo malignant development there occurs a deciduoma malignum. This view is that of the most recent observers, and distinctly adverse to the belief which considers deciduoma malignum an ordinary sarcoma of the uterus and hydatidiform mole as a myxoma of the chorionic villi.—ED.]

Acute Peritonitis without Known Cause Complicating Pregnancy and Labor.—In the *Transactions of the Obstetrical Society of London*, 1899, p. 389, PHILLIPS reports the following very interesting case. The patient was a woman, aged thirty-two years, who had one child, and was pregnant for the second time. She was uncertain regarding the period of pregnancy, but was probably between the sixth and seventh month. She fell, striking herself with considerable violence against the back of a chair on the left side of the abdomen. Violent sickness and severe pain followed. Up to this time she had been perfectly well, without vaginal discharge of any kind. The pain became so severe that medical attendance was summoned, and the patient was found to have a temperature of 103° F. and a pulse of 120. The pain started in the left iliac fossa and extended upward along the left side of the chest to the corresponding side of the head, also downward along the thigh. The uterus was contracting, and the internal os easily admitted two fingers. There was slight tenderness over a small area in the left iliac fossa. There was positively no evidence of peritonitis.

The patient was admitted to the British Lying-in Hospital, and opium was given and fomentations used to relieve the pain. Shortly afterward a living fœtus was expelled in the membranes, apparently without pains. Soon after labor the patient's pulse became 140, her respiration 30, while the abdomen was greatly distended. The placenta was expelled without bleeding. Obstinate vomiting continued.

The patient's condition demanded operation and the abdomen was opened. The intestines were greatly distended. The roof of the pelvis was covered with a thick, straw-colored membrane in patches. In both iliac fossæ there was a little semi-purulent fluid. The right Fallopian tube was purple red in color, smooth and glistening, and at the abdominal ostium was a large flake of lymph. On removing this the ostium was found to be patent. The uterus was purple in color, its surface covered with a few flakes of lymph. The left Fallopian tube seemed healthy. Both ovaries were swollen and their vessels engorged. The appendix was healthy, the ascending and descending colon full of soft feces. The peritoneal cavity was washed out with normal salt solution and a quart allowed to remain. The patient soon died.

Autopsy showed soft and purulent lymph in the lower portions of both pleuræ. There was general peritonitis, the intestines being glued together with purulent lymph. There was no rupture of stomach or intestines. Deep in the cervix there was a great deal of bruising and ecchymosis, but no sloughing. No purulent foci were found in the uterus, nor were its walls perforated. No focus of infection or cause of the peritonitis could be found. A bacteriological examination was not made.

The writer has collected five similar cases. In one of these drugs had been used to produce abortion, but nothing had been done to the uterus. This patient died of peritonitis, the abdomen containing fetid, purulent

fluid. Simpson reports the case of a woman at full term who came into labor. The first stage was long and progress very slow, and during the first stage the patient suddenly died. On autopsy peritonitis and agglutination of the intestines were found. No cause could be discovered. Romiti has described the case of a young primipara who was struck in the abdomen. Labor came on, and was quick and normal. Death soon followed. Upon autopsy about a quart of blood was found in the pelvic cavity, and in the left ovary a ruptured follicle with clot. The bleeding appeared to be the cause of the peritonitis. Gow saw the case of a multipara, who, a month before term, slipped through a hole in a rotten floor, injuring the abdomen. When labor came on she was suddenly seized with nausea and severe abdominal pain. The patient died undelivered, and post-mortem Cæsarean operation failed to save the child. On autopsy, peritonitis was present, for which no cause could be found.

In discussion it was suggested that the bacillus coli communis might have been forced through the wall of the intestine, causing the condition present.

Fibromyomata and Pregnancy.—In the *Zeitschrift für Geburtshülfe und Gynäkologie*, 1900, Band xlii., Heft 3, HOFMEIER contributes an interesting paper upon this subject.

Upon analyzing his statistics he finds myomatous tumors equally frequent among married and unmarried women. He does not believe that the myomatous tumor itself causes sterility. From the analysis of his cases he finds that very few of these patients during the pregnant condition required especial treatment, and that in very few would he be justified in operating during pregnancy. When, however, labor comes on in these cases, should delay occur and the patient seem threatened with exhaustion, operation should be undertaken at once. Where the patient can be delivered without hysterectomy, Hofmeier has not seen grave complications in the delivery of the placenta. In forty-two cases under his observation but two died, one suddenly from dilatation of the heart or embolus, and the other sixteen days after delivery of septic infection.

As regards cases in which the tumor is removed and the uterus allowed to remain, Hofmeier calls attention to the statistics of Engstroem. In twenty-two patients operated upon in this way pregnancy occurred subsequently in four.

[Our experience coincides largely with that of Hofmeier. In cases where the fibroid growth invades the greater portion of the uterus the physician must not expect prompt and vigorous labor, and should be prepared to operate in the interests of mother and child. When but one tumor is present delivery through the vagina may occur in spite of unfavorable indications. Forceps and version have been useful in a number of these cases in our experience. Attention must be directed to the danger of infection, and this is especially true when the placenta is attached at or near the site of the tumor. In such a case the placenta might not be delivered spontaneously, but would become partly separated, giving rise to bleeding. Should the patient become infected during the removal of the placenta, the septic poison would enter the sinuses of the womb and a rapid and violent process result.—ED.]

OPHTHALMOLOGY.

UNDER THE CHARGE OF

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AND

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Iodic-acid Solutions for Trachoma.—A. SCHIELE (Kursk) claims to have cured 78 out of 100 cases of this disease by applications of a watery solution of iodic acid (IO_3H). The solution used for pencilling the lids had the strength of 5 per cent. To drop into the eye, 2 or 3 per cent. solutions were used. The applications caused sharp pain. Experiments seem to show that such solutions penetrate and act deeply upon the diseased tissue.—*Centralblatt für praktische Augenheilkunde*, April, 1900.

Iodine Solutions for Trachoma.—H. H. SEABROOK (New York) has tried the treatment with iodine dissolved in a petroleum preparation, as recommended by Nesnamoff (see this JOURNAL for May, 1898). He finds that slight cases of granular lids may be cured in two or three weeks, while severe cases may require as many months, but the pannus begins to improve markedly in the first week or two. For mild cases the 1 per cent. solution is applied every other day; in more severe cases a 2 per cent. solution. Stronger solutions may be made by the addition of ether, but they are more painful. It is necessary that the iodine should penetrate the conjunctival surface, in order to produce the proper effect. In severe cases with frog-spawn granulations these were scarified or squeezed, and the iodine solution used as after-treatment.—*New York Eye and Ear Infirmary Reports*, January, 1900.

[Since noticing Nesnamoff's paper we have used this treatment and find it distinctly superior to many of the methods in common use. It is certainly worthy of much wider attention than it has yet received.—ED.]

Ocular Lesions of Typhoid Fever.—E. KOENIG (Paris) reports a case of optic neuritis and divergent strabismus without ptosis coming on at the end of the third week of typhoid fever. The patient was a woman, aged twenty-three years, who for three years had been subject to epileptic seizures. The fields of vision were concentrically contracted, and the right eye, which was in all respects the worse, had a relative central scotoma. The ophthalmoscopic appearances were those of retrobulbar neuritis rather than of choked disk.

M. ANTONELLI (Paris) reports congenital ocular defects in a child whose mother suffered from severe typhoid fever from the fourth to the sixth

month of her pregnancy. Both eyes presented anterior polar and cortical cataracts. There were nystagmus, gray, irregular optic disks, vascular changes, and pigment changes throughout the fundus. The child was the second of three, both the others being quite healthy. It was very small at birth and delicate, and the dentition had been somewhat irregular.

In discussing the above cases M. Boucheron said that choroidal hemorrhage was the common lesion of the eye in typhoid fever. The hemorrhage as such quickly disappeared, but the scar caused by it remained.—*Recueil d'Ophthalmologie*, February, 1900.

Visual Disturbances in Acromegaly.—W. A. HOLDEN (New York) finds that the gross changes in the optic chiasm occur in the following order:

First, the posterior portion of the chiasm is compressed by the pituitary body. Following this, the posterior and middle portions of the chiasm are flattened and forced upward, and thus separated from the anterior portion, which is protected by the bone beneath it. Later, with this tilting upward of the chiasm posteriorly and the forcing forward of the anterior wall of the pituitary fossa, the anterior portion of the chiasm is encroached upon by the pituitary body and arched directly forward. Finally, the chiasm may be severed completely.

Visual disturbances have been noted in about one-half of the reported cases. In over 50 per cent. of these there has been concentric contraction of the visual field, with diminution of central acuteness of vision. In somewhat less than 50 per cent. there has been bitemporal hemianopsia, absolute or for colors only, with or without some contraction of the nasal halves of the fields. In half a dozen cases there has been homonymous hemianopsia, absolute or for colors only; and in one case there was found binasal hemianopsia.

There is no special time for the appearance of visual symptoms in acromegaly. These come on, occasionally, soon after the enlargement of the extremities is noticed, but usually not until years after, and the disease may exist for ten or fifteen years without the appearance of any visual disturbance whatever.—*Archives of Neurology and Psychopathology*, vol. ii.

Hereditary Optic Atrophy.—R. D. BATTEN (London) reports three cases of this affection occurring in brothers exposed to lead-poisoning. All three were plumbers, but there was no sign of lead paralysis and no history of colic. Neither was there any history of other cases of blindness in the family. The toxic influence of alcohol and tobacco could not be excluded. But none of the cases showed any tendency to improvement under treatment and the withholding of these drugs. In one of the cases there occurred an acute neuritis.—*Ophthalmic Review*, June, 1900.

H. F. HANSELL (Philadelphia) reports a case of double acute retrobulbar neuritis occurring at the age of fifty-six years in a man, several of whose uncles and aunts became nearly blind in adult life, and who had two brothers in the same condition.—*American Journal of Ophthalmology*, June, 1900.

[The bilateral character of the lesions in these cases separates them from the ordinary form of retrobulbar optic neuritis. The failure to improve under treatment commenced early, while the exclusion of alcohol and tobacco

separates them from the more common form of toxic amblyopia. That even the most typical cases of hereditary optic atrophy may begin with retinitis or neuro-retinitis has been pointed out by some recent observers, so that both of the above writers are in harmony with the general trend of professional thought in recognizing the hereditary or family factor as an important one in causation.—ED.]

Treatment of Corneal Ulcers by Electrolysis.—FRANK CORNWALL (San Francisco) states there are ulcers of the cornea that at times have the appearance of being progressive, yet which remain for weeks, characterized by slight if any invasion, and in which photophobia and reflex neuralgia are very great. Electrolysis is indicated in these cases and also in what are called serpiginous ulcers. Its broadest field of usefulness, however, compared with any other method, is in chronic central ulcers which are very slight, the repair being almost complete.

In the treatment of these cases the voltage must be very low and the ampèreage not more than ½ milliampère. Operating under a magnifying lens the parts where the epithelial disturbance is greatest may be slightly touched with the end of the needle. If there are parts wherein Bowman's membrane seems involved, deeper and more thorough work will be needed, but caution should be exercised, and not too much done at one sitting.

Cornwall has given this treatment a trial in phlyctenular ulcers of the cornea, and the results have always been to aggravate the condition.—*Archives of Ophthalmology*, January, 1900.

The Analgesic and Therapeutic Value of Dionin.—A. DARIER (Paris) thinks his experiments have demonstrated that in dionin we possess an analgesic capable of relieving for many hours the most violent ocular pain in iritis, corneal ulcer, glaucoma, etc. He has employed it in 5 per cent. solution instilled into the conjunctival sac or injected beneath the conjunctiva. The 10 per cent. solution, he finds, is not stable. He has also used it by placing the powdered drug in contact with the conjunctiva. However applied, it at first causes severe burning pain and œdema of the part.—*La Clinique Ophthalmologie*, 1900, Nos. 6 and 7.

DAXENBERGER (Regensburg) reports two cases in which the severe reaction produced by applications of this drug continued as long as thirty-six hours.—*Wochenschrift für Therapie und Hygiene des Auges*, May 10, 1900.

A. GRAEFE (Berlin), from a trial of dionin in 200 cases, finds its influence is favorable in all affections of the cornea (except in the keratitis due to sarcoma), in conjunctival catarrh, acute or chronic, and in disease of the vitreous. It is also valuable associated with atropine in the treatment of iritis and irido-cyclitis, and probably also chorio-retinitis.—*Deutsche medicinische Wochenschrift*, March 22, 1900.

[All observers agree that dionin exerts a powerful influence over the nutrition of the eye and particularly over the lymph-circulation of the parts; and, so far, the only injurious effects recorded are the pain which occurs in all cases and the prolonged inflammatory reaction, which must be an unusual idiosyncrasy; but the œdema it causes might at times prove a serious complication.—ED.]

OTOLOGY.

UNDER THE CHARGE OF

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Vibratory Pneumomassage of the External Ear in Chronic Deafness.—OSTMANN (*Ann. des mal. de l'Oreille*, November, 1899) employs the electric masseur of Hirschmann, of Berlin, in application of *pneumatic* impulses to the membrana tympani in chronic hypertrophic otitis media. The massage is kept up for ten minutes at a time, and sometimes longer, every day for two weeks, from 1000 to 1200 impulses being applied at a sitting. He concludes that vibration massage (aërial) is indicated: (1) In chronic deafness consecutive to chronic hypertrophic otitis media. Before this treatment of the ear is applied Ostmann urges the necessity of treating all nasal, pharyngeal, and tubal lesions, in order to avoid a recurrence of disease in the middle ear. (2) In chronic deafness supervening upon acute catarrhal otitis media, defying all other treatment. Vibratory (pneumo) massage is contraindicated (1) in all acute inflammations of the conducting apparatus of the ear. (2) In all cases in which a lesion exists in the percipient apparatus of the ear, the conduction of sound remaining normal. (3) Considering its mode of action, pneumomassage is contraindicated in otitis media that has already induced impaction of the ossicles, or an extensive atrophy of the membrana tympani, or adhesions of the membrane with the promontory.

[It would seem from notes of four cases given by Ostmann that the hearing is greatly improved by the above mode of treatment continued daily for from two to four weeks.]

Acute Bi-cameral Brain Abscess After Opening the Mastoid; Recovery.—H. SELIGMAN (*Archives of Otology*, August, 1899) has reported the case of a young man, aged twenty years, the subject of a purulent otitis media since childhood. A mastoid trephination was performed, the indications for it not being given. Caries in the roof of the antrum was discovered and the diseased tegmen removed. Three days later symptoms of brain abscess, probably in the temporosphenoidal lobe, set in. On the eighth day the squama was trephined by chiselling, and after incision of the unpulsating dura a needle introduced into the brain upward and inward revealed the presence of pus at a depth of 3 cm. The abscess-cavity was then opened and its fetid contents washed out. The symptoms of brain pressure from abscess did not diminish, but rather increased, and included some tremor in the left hand, paraphasia, and then amnesic aphasia. On the eighteenth day after the first operation on the mastoid the symptoms of brain tension suddenly disappeared, with a simultaneous increase in the quantity of fetid pus in the dressings of the wound. It was, therefore, judged that an adjoining abscess had ruptured into the first one and had discharged itself out-

wardly. Muscular twitching ceased on the twentieth day, and on the thirty-sixth day the patient left his bed, but discharge of pus continued for some days after this date.

Cerebral Abscess Following Influenza Otitis.—VOUZELLE (*Ann. des mal. de l'Oreille*, September, 1898, p. 258) reports the occurrence of an abscess in the temporal lobe following an acute influenza otitis in a man aged twenty-six years. The man was trephined on two different occasions, but died. At the autopsy an abscess the size of a pigeon's egg was found in the temporal lobe in communication with the sphenoidal prolongation of the lateral ventricle by means of a narrow opening. The opening in the parietal region of the cranium did not enable the operator to reach the abscess, and after the autopsy Vouzelle concluded that trepanation of the mastoid should always be performed in the presence of grave general phenomena, even if the mastoid itself presents no symptoms of redness, tenderness, or swelling, because an otitic abscess of the brain must be sought for near the base of the petrous part of the temporal bone.

Unilateral Paralysis of Cerebral Nerves Produced by a Tumor Originating in the Maxillary Sinus.—MINGAZZINI and LOMBI (*Ann. des mal. de l'Oreille*, August, 1898, p. 173) report a case of paralysis on the left side of several cranial nerves due to a sarcoma originating in the left maxillary sinus, and, having destroyed the turbinated bones, encroached upon the naso-pharynx, and involved the cavernous sinus, implicating the cerebral nerves of that side. The symptoms, which existed only on the left side, consisted in anosmia, dimness of vision, complete ophthalmoplegia, anæsthesia of the trigeminus, paralysis of the facial, of the glosso-pharyngeal, and of the hypoglossal. The ophthalmoscopic examination was negative.

HYGIENE AND PUBLIC HEALTH.

UNDER THE CHARGE OF

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Diseases Due to Ingestion of Oysters and Other Mollusks, and their Prevention.—The occurrence of cases of typhoid fever in France, England, and America due to eating infected oysters led the French Government to institute an investigation of the causes of contamination and the manner of its occurrence in oyster beds. This was entrusted to Dr. MOSNY, who has now contributed an elaborate and important paper on the general subject of mollusk poisoning (*Revue d'Hygiene*, December, 1899, pp. 1057–1105; Janu-

ary, 1900, pp. 12–62; February, 1900, pp. 102–142; and March, 1900, pp. 193–212). He calls attention to the marked analogy in the symptoms observed in the numerous cases of illness caused by the ingestion of mollusks in general, from which it appears that the particular species plays no part, the mollusk being simply the passive agent by which the poison is conveyed. Certain pathogenic bacteria have been demonstrated beyond a doubt both in the tissues of the mollusks themselves and in the water retained between their shells, and experiments have proved that their vitality can be retained for a considerably longer time than that which ordinarily elapses between collection and sale to the public. The researches made in England, America, France, Germany, and Italy all throw light upon the origin and causes of contamination of oyster beds, and prove that the danger is neither as great nor as wide-spread as one is apt to fear, and that the trouble may be averted by transferring the beds, abandoning such as are exposed to contamination, or suppressing, when possible, the sources of infection.

Many of the very numerous cases of poisoning by mollusks are properly to be ascribed to decomposing specimens, just as is the fact in many cases of meat-poisoning, and these must be carefully separated from those due to the accidental presence of pathogenic organisms in fresh food materials. Some cases are idiosyncratic in character, for many persons cannot eat mussels from any source without evidence of serious disturbance, including headache, abdominal pain, nausea, vomiting, urticaria lasting from a few hours to several days, fainting, and delirium, just as others cannot eat crabs, lobsters, and various species of fish. In another class of cases of mussel poisoning individual predisposition plays no part, the symptoms appearing in all or almost all the persons who have eaten from the same lot. Of this class the well-known outbreak at Wilhelmshaven is a most striking example; all who ate, nineteen in number, were stricken, and four died. Here the cause was definitely ascertained to be a toxic alkaloidal substance in the liver of the mussel, and animal experimentation produced symptoms identical with those observed in the victims of the outbreak and closely analogous to the effects produced by curare. It was further shown that the mussels were poisonous only in the dock where they were gathered; that other forms of fish life from the same place were equally toxic, and that wholesome mussels placed in the dock became toxic in a short time and lost their poisonous properties rapidly after being returned to their original source. Hence, either the poison or its exciting cause must be held to reside in the water where the mussels were gathered.

Intolerance of certain persons for oysters is less commonly observed, and idiosyncrasy plays a much smaller part in the manifestation of disturbance from this cause. Cases of oyster poisoning may be divided into five classes, according to the symptoms. In the class in which nervous phenomena are predominant the symptoms remind one of curare poisoning. This type is extremely rare, always severe, and generally quickly fatal. The second class includes those cases in which the symptoms are gastro-intestinal. These cases are the most common, and least lasting and serious. The symptoms, which include violent colic, cold sweats, pericardial pain, and nausea, with or without vomiting, appear suddenly. In some cases the liquid, bilious stools persist, without colic, as long as four or five days. In the third class

the gastro-intestinal phenomena assume a very severe character, and suggest more or less strongly the clinical picture of dysentery. In these cases the dysenteric symptoms appear somewhat tardily, but persist for a long time. In the fourth class the cases are choleriform in character, and in a number of instances have been considered as cases of true Asiatic cholera. The fifth class includes the very numerous cases of undoubted typhoid fever, of which the outbreak at Wesleyan College in 1894, so completely and scientifically investigated by Conn, is the most conspicuous illustration.

Regarding the common notion that oysters at the breeding season are poisonous, attention is called to the fact that cases ascribed to this supposed influence may be otherwise explained, and that the people in the neighborhood of oyster beds eat them habitually at all seasons without injury. Thorough etiological research in every case of oyster poisoning investigated has shown that the oysters came from beds contaminated by sewage matters. But two explanations are possible in cases of poisoning by mollusks: they are due either to a toxic substance or to bacteria in the tissue of the mollusk or in the water between its shells, and the remote cause is always sewage contamination.

The bacteria of cholera and typhoid fever, the *B. coli communis*, the *proteus vulgaris*, and other organisms have been found in oysters from contaminated beds. The presence of the colon bacillus should always arouse suspicion and induce improvement in the management and supervision of the beds. Chantemesse has shown that oysters immersed for twenty-four hours in salt water contaminated with typhoid dejections or cultures and kept unopened for a day after removal will yield the organisms of the disease. According to Boyce, the typhoid bacillus does not grow in the tissues of the oysters, but disappears in from one to seven days after the oysters are placed in pure sea water; but, according to Foote, under conditions of continued immersion in contaminated water they multiply in the tissues during the first two weeks and then diminish, but can still be found after thirty days. In the opinion of Mosny the usual period of eight days in pure sea water is sufficient for their disappearance. The cholera organism has been found by Klein four days after removal of the oysters from water purposely contaminated with them, while De Giaxa has found them to be destroyed in from six to forty-eight hours. The bacilli of anthrax have been known to retain their vitality in sterilized sea water for twenty-five days, and the spores even as long as nineteen months. The *staphylococcus aureus* appears to have a vitality equal to that of anthrax bacilli. The *proteus vulgaris*, the pneumococcus of Friedländer, and certain other pathogenic organisms have been found active after forty days.

The two most important causes of unsanitary conditions of oyster beds are proximity to the mouth of rivers and the vicinity of seaports. Rivers are likely to undergo a process which we know as self-purification, which rids them after a time of pathogenic germs thrown into them with sewage. This purification of streams is susceptible of considerable modification through the influence of the sea, which at times interferes seriously. It is necessary for the best sanitary condition of beds situated at the mouth of rivers that the water of these rivers be sufficiently purified at that point in its flow where marine influences make themselves felt. No general law is equally appli-

cable to all rivers, and, therefore, it is necessary to determine in each case the average degree of purification at the boundary line of the zones of land and marine influence. Beds situated at the mouth of rivers flowing into seas in which tides are either absent or insignificant in their influence, such as the Baltic and Mediterranean, can be considered as free from possible contamination only when so far removed from sources of pollution that the currents, whatever their direction, cannot carry contamination to them. This distance varies widely according to the various local conditions of currents, prevailing winds, and force thereof, etc., and must be determined in each case. In the case of beds situated at river mouths where there is tidal influence it is important that sewers should not empty themselves into the river excepting during the first half of ebb tide, since it is important that the sewage shall be carried out to sea before the flood tide shall have an opportunity to bring it back again; and it is important that the beds shall be laid out above the level of low water in such a manner that they will remain uncovered during the latter half of the ebb and during the first half of the flood. When the beds are not situated in the channel of the river itself, but in its banks, it should be required of the proprietor that he shall not allow the river water to enter the beds excepting at high tide or during the hours of ebb tide when the sewage thrown into the river is below the entrance to the conduits by which water is admitted to the beds.

It is, of course, very evident that these general rules must be modified according to each case, since the conditions of contamination and purification vary according to the distance from the sources of pollution and according to the nature and degree of contamination, the size of the estuary, the situation of the beds, the zone of influence of the tide, etc.

Many of the English beds are notoriously contaminated. The installation and management of the English oyster beds situated near river mouths should not, as a rule, be regarded as models. The French beds are far more satisfactorily placed, though with certain of them the surroundings are not beyond improvement. In all cases of pollution the source of the contaminating matters should, when possible, be suppressed; when this is not possible the beds should be removed. Beds in good sanitary locations and condition must be protected against any possible cause of pollution.

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